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From: Kwon, Brian-Yong
Sent: Thursday, July 22, 2004 9:33 PM
To: STIC-ILL
Subject: 09/980824

1. "phase I/II trial of dexverapamil, epirubicin and granulocyte/macrophage-colony-stimulating factor in patients with advanced pancreatic adenocarcinoma", Scheithauer et al., Journal of Cancer Research and Clinical Oncology, 1995, 121 (Supp. 3, Dexverapmail: A clinical approach to circumventio of multidrug resistance in cancer), R7-R10.

2. Phae II trial of dexverapamil and epirubicin in patients with non-responsive metastatic breast cancer", Lehnert et al., British Journal of cancer, 1998, 77(7), 1155-1163.

3. "effect of D,L-verapamil, verapamil enantiomers and verapamil metabolites on binding of vincristine to alpha-acid glycoprotein", Woodcock et al, Eur. J. Cancer, Part A, 1993, 29A(4), 559-61.

4. "R-verapamil decreases antiestrogen resistance in a breast cancer model", Kellen et al., Anticancer Research, 1991, 11 (2), 809-11.

5. "eFFECT OF r-VERAPAMIL ON PHARMACOKINETICS OF PACLITAXEL IN WOMEN with breast cancer", Berg et al,, Journal of clinical Oncology, 1995, 13(8), 2039-42.

6. "intestinal secreation of intravenous talinolol is inhibited by liminal R-verapamil", Gramatte et al, Clinical Pharmacology & Therapeutics, 1999, 66(3), 239-245.

7. "treatment of advanced colorectal cancer with doxorubin combined with two potential multidrug-resitance-reversing agents, High-dose oral tamoxifen and dexverapamil", Jouranl of Cancer Research and Clinical Oncology, 1997, 123(8), 452-455.

8. "inhibition of p-glycoprotein-mediated vinblastine transport across HCT-8 intestinal carcinoma monolayers by verapamil, cyclosporine,...", Zacherl et al., Cancer cheotherapy and Pharmacology, 1994, 34(2), 125-32.

Brian Kwon
REM 4B81
Patent Examiner, Pharm-D.
(571)272-0581

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      FILE 'REGISTRY' ENTERED AT 19:37:31 ON 22 JUL 2004
L1             3 S R-VERAPAMIL OR R-GALLOPAMIL
L2             0 S GGALOPAMIL
L3             0 S GALOPAMIL
L4             8 S GALLOPAMIL

      FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE' ENTERED AT 19:39:53 ON 22 JUL 2004
L5         95720 S 38321-02-7/RN OR R-VERAPAMIL OR D-VERAPAMIL OR DEXVERAPAMIL O
L6          3318 S VERAPAMIL (L) (DERIVATIVES OR ANALOGUES OR ANALOGS OR METABOL
L7         95720 S L6 OR L5
L8           364 S L7/THUR
L9            67 S L8 AND (TUMOUR OR CANCER OR TUMOR OR INTESTINE  OR CHEMO-)
L10            1 S L9 AND GLUCURONIDASE
L11           67 FOCUS L9 1-

=> s l11 and (dexverapamil or verapamil)
L12           66 L11 AND (DEXVERAPAMIL OR VERAPAMIL)

=> focus l12
PROCESSING COMPLETED FOR L12
L13           66 FOCUS L12 1-

=> d ibib abs 1-66

L13  ANSWER 1 OF 66  CAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         1993:160578  CAPLUS
DOCUMENT NUMBER:          118:160578
TITLE:                    Effect of D,L-verapamil, verapamil
                          enantiomers and verapamil metabolites on the
                          binding of vincristine to α1-acid glycoprotein
AUTHOR(S):                Woodcock, Barry G.; Abdel-Rahman, Mahran S.; Wosch,
                          Frank; Harder, Sebastian
CORPORATE SOURCE:         Dep. Clin. Pharmacol., Johann Wolfgang Goethe-Univ.,
                          Frankfurt/Main, D 6000, Germany
SOURCE:                   Eur. J. Cancer, Part A (1993), 29A(4), 559-61
                          CODEN: EJCTEA
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB    Vincristine binding to solns. of α1-acid glycoprotein (AGP, 2 mg/mL)
      and the effect of D,L-verapamil, verapamil enantiomers
      and the verapamil metabolites norverapamil and D617 were
      investigated in vitro using equilibrium dialysis and 3H-labeled vincristine.
      Vincristine binding to AGP (52.3 ± 3.6%) was concentration independent over
      the range 0.002-2.0 μg/mL.  The displacement of vincristine from AGP
      varied between 25.1 and 81.3% with D,L-verapamil and
      verapamil enantiomers added at concns. in the range 5-50 μg/mL.
      In contrast, the displacement by D617 (5-100 μg/mL) was weaker and
      varied between 0 and 47%.  The displacement at 20 μg/mL produced by
      D,L-verapamil, R-verapamil, S-verapamil and
      norverapamil was 53.1%, 56.8%, 58.9% and 53.9%, resp., was more than
      double that for D617 (25%; P = 0.002).  It is concluded that vincristine,
      D,L-verapamil and verapamil isomers and metabolites
      interact at binding sites on AGP.  These interactions may be clin.
      important in multidrug resistance, for example in cancer
      patients with elevated levels of AGP undergoing treatment with
      verapamil and vinca alkaloids.

L13  ANSWER 2 OF 66  CAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         1991:526552  CAPLUS
DOCUMENT NUMBER:          115:126552
TITLE:                    R-verapamil decreases antiestrogen
                          resistance in a breast cancer model
AUTHOR(S):                Kellen, J. A.; Wong, Aileen; Georges, E.; Ling, V.
```

CORPORATE SOURCE: Sunnybrook Health Sci. Cent., Univ. Toronto, Toronto, ON, M4N 3M5, Can.
SOURCE: Anticancer Research (1991), 11(2), 809-11
CODEN: ANTRD4; ISSN: 0250-7005
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Drug resistance eventually limits the effectiveness of antiestrogens in breast **cancer** treatment. Pharmacol. reversal of this refractoriness has been attempted with (R)-**verapamil**, a well tolerated calcium channel blocker. This drug significantly decreased the incidence of lung foci after i.v. seeding of the R3230AC rat adenocarcinoma; this effect was correlated with reduction in the expression of P-glycoprotein. The simultaneous administration of anti-estrogens with a non-toxic enantiomer of **verapamil** was beneficial in the **tumor** model investigated.

L13 ANSWER 3 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:246218 CAPLUS
DOCUMENT NUMBER: 128:317041
TITLE: Phase II trial of **dexverapamil** and epirubicin in patients with non-responsive metastatic breast **cancer**
AUTHOR(S): Lehnert, M.; Mross, K.; Schueller, J.; Thuerlimann, B.; Kroeger, N.; Kupper, H.
CORPORATE SOURCE: Department C of Internal Medicine, Kantonsspital St Gallen, St Gallen, 9007, Switz.
SOURCE: British Journal of Cancer (1998), 77(7), 1155-1163
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Agents capable of reversing P-glycoprotein-associated multidrug resistance have usually failed to enhance chemotherapy activity in patients with solid **tumors**. Based on its toxicity profile and exptl. potency, **dexverapamil**, the R-enantiomer of **verapamil**, is considered to be promising for clin. use as a chemosensitizer. The purpose of this early phase II trial was to evaluate the effects of **dexverapamil** on epirubicin toxicity, activity and pharmacokinetics in patients with metastatic breast **cancer**. A two-stage design was applied. Patients first received epirubicin alone at 120 mg m-2 i.v. over 15 min, repeated every 21 days. Patients with refractory disease continued to receive epirubicin at the same dose and schedule but supplemented with oral **dexverapamil** 300 mg every 6 h + 13 doses. The Gehan design was applied to the **dexverapamil** /epirubicin cohort of patients. Thirty-nine patients were entered on study, 25 proceeded to receive epirubicin plus **dexverapamil**. **Dexverapamil** did not increase epirubicin toxicity. The dose intensity of epirubicin was similar when used alone or with **dexverapamil**. In nine intrapatient comparisons, the area under the plasma concentration-time curve (AUC) of epirubicin was significantly reduced by **dexverapamil** (mean 2968 vs 1901 μg ml-1 h-1, P = 0.02). The mean trough plasma levels of **dexverapamil** and its major metabolite nor-**dexverapamil** were 1.2 and 1.5 μM resp. The addition of **dexverapamil** to epirubicin induced partial responses in 4 of 23 patients evaluable for **tumor** response (17%, CI 5-39%, s.e.p 0.079). The remissions lasted 3, 8, 11 and 11+ months. These data suggest that the concept of enhancing chemotherapy activity by adding chemosensitizers may function not only in haematol. malignancies but also in selected solid **tumors**. An increase in the AUC and toxicity of cytotoxic agents does not seem to be a prerequisite for chemosensitizers to enhance anti-**tumor** activity.
REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:131901 CAPLUS
DOCUMENT NUMBER: 112:131901
TITLE: The activity of **verapamil** as a resistance modifier in vitro in drug resistant human **tumor** cell lines is not stereospecific
AUTHOR(S): Plumb, Jane A.; Milroy, Robert; Kaye, Stanley B.
CORPORATE SOURCE: Dep. Med. Oncol., Univ. Glasgow, Glasgow, G61 1BD, UK
SOURCE: Biochemical Pharmacology (1990), 39(4), 787-92
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The L-isomer of **verapamil** is a more potent calcium antagonist than the D-isomer. The two stereoisomers of **verapamil** were examined for their ability to increase the chemosensitivity in vitro of three drug resistant cell lines (2780AD, MCF7/AdrR and H69LX10). Neither racemic **verapamil** nor its individual isomers had any effect on the drug sensitivity of the parent cell lines (A2780, MCF7 and NCI-H69). **Verapamil** increased the sensitivity of all three resistant cell lines to adriamycin by 10-12-fold. This activity was concentration-dependent and was maximal at 6-7 μM. The increase in sensitivity was only 2-3-fold at 2 μM, the maximum plasma concentration achieved in patients. Both the D- and L-isomers of **verapamil** alone at 6.6 μM were as effective as racemic **verapamil** and the D-isomer demonstrated the same concentration-dependent activity as racemic **verapamil**. The total cellular adriamycin concentration in both 2780AD and MCF7/AdrR was increased by 2-fold in the presence of **verapamil** (6.6 μM). Both D- and L-**verapamil** alone increased the amount of drug accumulated to the same extent as racemic **verapamil**. Thus, the resistance modification by **verapamil** is not stereospecific. The use of D-**verapamil** alone in patients could increase the maximum tolerated plasma concns. of **verapamil**. D-**Verapamil** may be a more effective resistance modifier in vivo than racemic **verapamil**.

L13 ANSWER 5 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:327308 CAPLUS
DOCUMENT NUMBER: 139:223696
TITLE: Enantioselective transport and CYP3A4-mediated metabolism of R/S-**verapamil** in Caco-2 cell monolayers
AUTHOR(S): Engman, Helena; Tannergren, Christer; Artursson, Per; Lennernas, Hans
CORPORATE SOURCE: Department of Pharmacy, Uppsala University, Uppsala, SE-751 23, Swed.
SOURCE: European Journal of Pharmaceutical Sciences (2003), 19(1), 57-65
CODEN: EPSCED; ISSN: 0928-0987
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have evaluated the passive and carrier-mediated intestinal transport and CYP3A4-mediated metabolism of R/S-**verapamil** with respect to dose dependency and enantioselectivity in modified Caco-2 cells. The present in vitro results were compared to published data from human in vivo and rat in situ jejunal perfusions with R/S-**verapamil**. Caco-2 cell permeability to enantiomers of **verapamil** and norverapamil was weakly concentration dependent (2.5-100 μM). While Caco-2 permeability to **verapamil** was 2.6- to 3.7-fold lower than in the human jejunum, it was 1.4- to 2.3-fold higher than in rats. However, all three models classified R- and S-**verapamil** as high permeability compds.

according to the biopharmaceutical classification system. In accordance with human and rat data, R/S-**verapamil** was transported to a minor extent by carrier-mediated mechanisms in Caco-2 cells. Neither the passive nor the carrier-mediated permeability was enantioselective in any of the three models. CYP3A4-mediated demethylation to R/S-norverapamil was enantioselective in Caco-2 cells. Apparent Vmax and Km values for the conversion of R-**verapamil** were 3.2 pmol/min/insert and 0.7 μM, resp., and for S- **verapamil**, 5.4 pmol/min/insert and 0.6 μM, resp. The enantioselectivity in the CYP3A4-metabolism observed in Caco-2 cells was in agreement with human data, but not with rat data, indicating that Caco-2 cells better reflect the human small **intestine** in this regard. However, all three models suggested that intestinal permeability to **verapamil** is unaffected by CYP3A4-activity. In summary, modified Caco-2 cells and human jejunum were qual. related with respect to R-and S-**verapamil** transport and CYP3A4-metabolism

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:21294 CAPLUS
DOCUMENT NUMBER: 130:246224
TITLE: Modulation by dietary salt of **verapamil** disposition in humans
AUTHOR(S): Darbar, Dawood; Fromm, Martin F.; Dell'Orto, Simonetta; Kim, Richard B.; Kroemer, Heyo K.; Eichelbaum, Michel; Roden, Dan M.
CORPORATE SOURCE: Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, Nashville, TN, 37232-6602, USA
SOURCE: Circulation (1998), 98(24), 2702-2708
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **intestine** is an increasingly well-recognized site of first-pass drug metabolism In this study, the authors determined the influence of dietary salt on the steady-state disposition of **verapamil**, a drug that undergoes extensive first-pass metabolism Eight normal volunteers received 120 mg of racemic **verapamil** orally twice a day for 21 days. The disposition kinetics of **verapamil** enantiomers were determined after coadministration of i.v. deuterated **verapamil** with the morning oral dose on days 7, 14, and 21. Each study day was preceded by 7 days on a fixed-salt diet: in 5 subjects, the initial study was conducted during a low-salt (10 mEq/d) diet, the second study during a high-salt (400 mEq/d) diet, and the third during a low-salt diet, whereas in the other 3 subjects, the sequence of diets was reversed. Plasma concns. of both unlabeled enantiomers (ie, from oral therapy) were significantly ($P<0.05$) lower during the high-salt phase (eg, mean area under the time-concentration curve [0 to 12 h] for S-**verapamil**: 7765±2591 ng · min · mL-1 [high salt] vs. 12 514±3527 ng · min · mL-1 [low salt], $P<0.05$). Peak plasma concns. were significantly lower and the extent of PR interval prolongation significantly blunted with the high-salt diet. In contrast, data with labeled drug (ie, reflecting the i.v. route) were nearly identical for the 2 diets. These data indicate that a clin. important component of presystemic drug disposition occurs at the prehepatic (presumably intestinal) level and is sensitive to dietary salt.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:527243 CAPLUS
DOCUMENT NUMBER: 125:237912

TITLE: Randomized trial of vindesine and etoposide ± **dexverapamil** in advanced non-small cell lung **cancer**. First results
AUTHOR(S): Gatzemeier, U.; Schneider, A.; V. Pawel, J.
CORPORATE SOURCE: Department Thoracic Oncology, Hospital Grosshansdorf, Hamburg, D-22927, Germany
SOURCE: Journal of Cancer Research and Clinical Oncology (1995), 121(Suppl. 3, Dexverapamil: A clinical approach to circumvention of multidrug resistance in cancer), R17-R20
CODEN: JCROD7; ISSN: 0171-5216
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The impact of **dexverapamil** (D) on the chemotherapy resistance of non-small cell lung **cancer** was investigated in a study of D plus chemotherapy vs. chemotherapy alone. Chemotherapy consisted of i.v. vindesine 3 mg/m2 bolus on days 1 and 5 and etoposide 140 mg/m2 on days 2 and 4. 1800 Mg D were given for 6 days. Cycles were repeated 3 weekly up to 4 courses. Cardiovascular side effects were more marked in the group receiving D. There were 5 partial remissions (31.3%) and 9 no changes (56.3%) in the group with D as opposed to 2 partial remissions (11.1%) and 6 no changes in the group without D.

L13 ANSWER 8 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:401232 CAPLUS
DOCUMENT NUMBER: 129:130954
TITLE: Phase II study of **dexverapamil** plus anthracycline in patients with metastatic breast **cancer** who have progressed on the same anthracycline regimen
AUTHOR(S): Warner, Ellen; Hedley, David; Andrulis, Irene; Myers, Robert; Trudeau, Maureen; Warr, David; Pritchard, Kathleen I.; Blackstein, Martin; Goss, Paul E.; Franssen, Edmee; Roche, Kathie; Knight, Shelagh; Webster, Sheila; Fraser, Ruth-Anne; Oldfield, Stephanie; Hill, Wendy; Kates, Robert
CORPORATE SOURCE: Toronto Sunnybrook Regional Cancer Centre, University of Toronto, Toronto, ON, M4N 3M5, Can.
SOURCE: Clinical Cancer Research (1998), 4(6), 1451-1457
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study evaluated whether metastatic breast **cancer** that has progressed on an anthracycline-containing drug regimen would subsequently respond to the identical regimen if **dexverapamil**, a modulator of P-glycoprotein-mediated drug resistance, is given concomitantly. Patients received 180 mg **dexverapamil**/m2 every 6 h for 15 doses, with the anthracycline administered 30 min after the 7th dose. There were 2 partial responses (10%), both of which lasted for 6 mo, and 2 addnl. patients had stable disease. Seven patients had asymptomatic cardiotoxicity consisting of hypotension (24%), bradycardia (5%), or prolongation of the P-R interval (14%). Two patients developed acute congestive heart failure, one on **dexverapamil** and one 10 days after stopping it. **Dexverapamil** did not seem to increase anthracycline toxicity. The median plasma trough **dexverapamil** plus norverapamil level on day 3 was 1110 ng/mL (range, 186-3385 ng/mL), and the median peak level was 2164 ng/mL (range, 964-8382 ng/mL). There was poor correlation between the values of mdr-1 expression as determined by reverse transcription-PCR and image cytometry. Because **dexverapamil** has been shown to affect doxorubicin pharmacokinetics, it cannot be concluded that the responses seen were necessarily due to P-glycoprotein inhibition. Addnl. studies are

necessary to determine whether mdr-1 modulators can reverse clin. drug resistance in breast **cancer** patients. The intrinsic cardiotoxicity of **dexverapamil** makes it less suitable for such studies than several other available agents.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 9 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:736792 CAPLUS
DOCUMENT NUMBER: 123:160022
TITLE: Effect of R-**verapamil** on the pharmacokinetics of paclitaxel in women with breast **cancer**
AUTHOR(S): Berg, Stacey L.; Tolcher, Anthony; O'shaughnessy, Joyce A.; Denicof, Andrea M.; Noone, Marianne; Ognibene, Frederick P.; Cowan, Kenneth H.; Balis, Frank M.
CORPORATE SOURCE: Pediatric and Medicine Branches, National Cancer Inst., Bethesda, MD, USA
SOURCE: Journal of Clinical Oncology (1995), 13(8), 2039-42
CODEN: JCONDN; ISSN: 0732-183X
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To study the effect of the multidrug-resistance reversal agent R-**verapamil** on the pharmacokinetic behavior of paclitaxel. Six women with breast **cancer** who received paclitaxel as a 3-h infusion with and without R-**verapamil** were monitored with frequent plasma sampling up to 24 h postinfusion. Paclitaxel concns. were measured using a reverse-phase high-pressure liquid chromatog. assay. Concomitant administration of R-**verapamil** resulted in a decrease in mean (± SD) paclitaxel clearance from 1789 ± 67 mL/min/m2 to 90 ± 34 mL/min/m2 ($P < 0.03$) and a 2-fold increase in paclitaxel exposure (area under the curve [AUC]). The mean end-infusion paclitaxel concentration was also 2-fold higher: 5.1 ± 1.8 μmol/L vs. 11.3 ± 4.1 μmol/L ($P < 0.03$). The alteration in paclitaxel pharmacokinetics when paclitaxel and R-**verapamil** are coadministered complicates the interpretation of response and toxicity data from clin. trials of this drug combination.

L13 ANSWER 10 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:657061 CAPLUS
DOCUMENT NUMBER: 132:30599
TITLE: Intestinal secretion of intravenous talinolol is inhibited by luminal R-**verapamil**
AUTHOR(S): Gramatte, Thomas; Oertel, Reinhard
CORPORATE SOURCE: Institute of Clinical Pharmacology, Medical School, University of Technology Dresden, Dresden, Germany
SOURCE: Clinical Pharmacology & Therapeutics (St. Louis) (1999), 66(3), 239-245
CODEN: CLPTAT; ISSN: 0009-9236
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: To examine the secretion of the β1-adrenergic receptor antagonist talinolol into the small **intestine** during its i.v. administration and to show the relevance of the P-glycoprotein-modulating drug **verapamil** for this secretory transport mechanism in humans. Methods: In 6 healthy volunteers, the intestinal steady-state perfusion technique (triple lumen tubing system) was used for measuring the appearance of talinolol within the small **intestine** while the drug was infused i.v. During 4 of the 7 perfusions performed, the perfusion fluid was changed from a **verapamil**-free solution and

talinolol appearance was measured while a R-**verapamil**-containing solution (565 μmol/L) was perfused. Results: Talinolol was transported into the intestinal lumen up to a concentration gradient between lumen and blood of .apprx.5.5:1. While perfusing the small **intestine** with a **verapamil**-free solution, the intestinal secretion rate of talinolol ranged from 1.94 to 6.62 μg/min per 30 cm length of the **intestine** (median values). Perfusion of a R-**verapamil**-containing perfusion fluid resulted in lower secretion rates (0.59-3.71 μg/30 cm·min), corresponding to 29%-56% of the values obtained without **verapamil** supplied intraluminally. Conclusion: I.v. administered talinolol is actively secreted into the human small **intestine**. This secretion is reduced by the intraluminal supply of the P-glycoprotein-modulating drug R-**verapamil**. This gives further rationale for P-glycoprotein-mediated intestinal drug secretion as a cause for incomplete oral bioavailability and for drug interactions during intestinal absorption.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 11 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:213953 CAPLUS

DOCUMENT NUMBER: 131:53590

TITLE: Unexpected effect of **verapamil** on oral bioavailability of the β-blocker talinolol in humans

AUTHOR(S): Schwarz, Ute I.; Gramatte, Thomas; Krappweis, Jutta; Berndt, Annette; Oertel, Reinhard; Von Richter, Oliver; Kirch, Wilhelm

CORPORATE SOURCE: Institute of Clinical Pharmacology, Faculty of Medicine, University of Technology, Dresden, Germany

SOURCE: Clinical Pharmacology & Therapeutics (St. Louis) (1999), 65(3), 283-290
CODEN: CLPTAT; ISSN: 0009-9236

PUBLISHER: Mosby, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effect of oral **verapamil**, a calcium channel blocker and potent inhibitor of P-glycoprotein, on pharmacokinetics of the β1-adrenergic receptor antagonist talinolol, a substrate of P-glycoprotein, was studied. In a randomized, crossover placebo-controlled study, oral pharmacokinetics of talinolol (50 mg) after concomitant administration of single doses of R-**verapamil** (120 mg) or placebo were investigated in 9 healthy volunteers. Concns. of talinolol, **verapamil**, and its main metabolite norverapamil were measured in serum with HPLC. Concns. of talinolol were also measured in urine by HPLC. Standard pharmacokinetic parameters were calculated with noncompartmental procedures. The area under the concentration-time curve for talinolol from 0 to 24 h was significantly decreased after R-**verapamil** vs. placebo (721 ± 231 ng · h · mL-1 vs. 945 ± 188 ng · h · mL-1; P < .01). Maximum serum concentration of talinolol was reached significantly earlier after R-**verapamil** compared with placebo (P < .05). Coadministration of R-**verapamil** did not affect the renal clearance or half-life of talinolol. Serum pharmacokinetics are paralleled by the results derived from urine concns. of talinolol. This is the first study to show a decreased oral bioavailability of a P-glycoprotein substrate (talinolol) in humans as a result of coadministration of **verapamil**. This effect is assumed to be caused by changes of the intestinal net absorption of talinolol because its renal clearance remains unaffected by administration of R-**verapamil**. This unexpected effect of R-**verapamil** is most likely dose-dependent as a result of an interplay between intestinal P-glycoprotein and gut metabolism

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 12 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:527241 CAPLUS
DOCUMENT NUMBER: 125:212097
TITLE: Phase I/II trial of **dexverapamil**, epirubicin and granulocyte/macrophage-colony-stimulating factor in patients with advanced pancreatic adenocarcinoma
AUTHOR(S): Scheithauer, W.; Kornek, G.; Raderer, M.; Koperna-Mach, K.; Mueller, C.; Karner, J.; Kastner, J.; Tetzner, C.
CORPORATE SOURCE: Medical School, Vienna University, Vienna, A-1090, Austria
SOURCE: Journal of Cancer Research and Clinical Oncology (1995), 121(Suppl. 3, Dexverapamil: A clinical approach to circumvention of multidrug resistance in cancer), R7-R10
CODEN: JCROD7; ISSN: 0171-5216
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A new anticancer chemotherapy was investigated in previously untreated patients with locally advanced of metastatic adenocarcinoma of the pancreas in a phase I/II study. Treatment consisted of oral **dexverapamil** (D) 1000 - 1200 mg/day for 3 days, epirubicin (E) given as an i.v. bolus injection on day 2 with a starting dose of 90 mg/m2, and 400 μg granulocyte/macrophage-colony-stimulating factor (GM-CSF) administered s.c. from day 5 through 14. E dose escalation levels were 90, 105, 120, and 135 mg/m2 . Treatment cycles were repeated every 3 wk. Hematol. toxicity, specifically granulocytopenia constituted the dose-limiting toxicity with a maximum tolerated dose of 120 mg/m2 for epirubicin. Despite routine supportive therapy with GM-CSF, 4, 2, and 5 patients experienced grade 4 granulocytopenia during their first 2 treatment courses at levels of 105, 120, and 135 mg/m2 . Non-hematol. toxicity was uncommon, generally modest, and did demonstrate a unclear relationship with the anthracycline dose. D-related cardiovascular symptoms occurred frequently, but they never resulted in serious toxicity requiring active medical intervention or permanent discontinuation of therapy. The recommended dose of E for this regimen with D and GM-CSF is 120 mg/m2 every 3 wk.

L13 ANSWER 13 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:646243 CAPLUS
DOCUMENT NUMBER: 121:246243
TITLE: Absorption enhancement of hydrophilic compounds by **verapamil** in Caco-2 cell monolayers
AUTHOR(S): Sakai, Michinori; Noach, Arthur B. J.; Blom-Roosemalen, Margret C. M.; de Boer, Albertus G.; Breimer, Douwe D.
CORPORATE SOURCE: Leiden/Amsterdam Center for Drug Research, Leiden University, Leiden, NL-2300, Neth.
SOURCE: Biochemical Pharmacology (1994), 48(6), 1199-210
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Caco-2 monolayers were used to determine whether **verapamil** enhanced the transport of hydrophilic compds. across epithelial cells. Transepithelial elec. resistance (TEER) measurements, as an indicator of the opening of tight junctions, and transport expts. with fluorescein-Na (Flu) and FITC-dextran Mw 4000 (FD-4) were used to assess the effect. (±)**Verapamil** concns. up to 3 + 10-4M increased TEER dose-dependently, whereas from concns. of 7 + 10-4 M onwards a dose-dependent drop was found. After removal of **verapamil** (<10-3 M) the effects on TEER were reversible within 30 min. A second

administration of **verapamil** after different time intervals produced a much larger effect on TEER than the first administration. The sep. R- and S-enantiomers did not reveal a difference in enantiomer effect. (±)**Verapamil** at 7 + 10-4 M increased Flu transport about 13-fold and 26-fold after the first and second treatment in the same monolayers, resp. Transport of FD-4 increased approx. 4-fold and 6-fold after the first and second treatment, resp. Potential damaging effects were assessed by trypan blue exclusion (cell death) and cell detachment. No cell death occurred at **verapamil** concns. of 8.5 + 10-4 M or lower, whereas cell detachment did not occur within 1 h at all concns. used in these expts. At later times detachment was observed at concns. of 7 + 10-4 M and higher. Confocal laser scanning microscopy showed that **verapamil** opens the paracellular route, thereby enhancing the permeability of hydrophilic compds. However, relatively high concns. are needed to achieve this effect and only a narrow concentration range can be used without cytotoxic effects, which limits the potential application of **verapamil** as an absorption enhancing agent.

L13 ANSWER 14 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:269870 CAPLUS
DOCUMENT NUMBER: 140:247075
TITLE: Treatment of abnormal increases in gastrointestinal motility with (R)-**verapamil**
INVENTOR(S): Kelly, John; Devane, John
PATENT ASSIGNEE(S): Ire.
SOURCE: U.S. Pat. Appl. Publ., 20 pp., Cont.-in-part of U.S. Pat. Appl. 2003 92,765.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004063784	A1	20040401	US 2002-294692	20021115
US 2003092765	A1	20030515	US 2002-256261	20020927

PRIORITY APPLN. INFO.: US 2002-256261 B2 20020927
US 2001-335959P P 20011115

AB The invention discloses methods for treating, preventing, and/or managing abnormal increases in gastrointestinal motility, and intestinal conditions that cause the same. Such conditions include, but are not limited to, irritable bowel syndrome, infectious diseases of the small and large **intestines**, and symptoms of any of the foregoing. In particular, the invention discloses methods of using enriched (R)-**verapamil**, as well as compns. and formulations containing the same.

L13 ANSWER 15 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:189208 CAPLUS
DOCUMENT NUMBER: 128:265706
TITLE: Gut wall metabolism of **verapamil** in older people: effects of rifampicin-mediated enzyme induction
AUTHOR(S): Fromm, Martin F.; Dilger, Karin; Busse, Dagmar; Kroemer, Heyo K.; Eichelbaum, Michel; Klotz, Ulrich
CORPORATE SOURCE: Dr Margarete Fischer-Bosch-Institut fur Klinische Pharmakologie, Stuttgart, 70376, Germany
SOURCE: British Journal of Clinical Pharmacology (1998), 45(3), 247-255
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Prehepatic metabolism of **verapamil** and its inducibility by rifampicin were investigated in older subjects. Eight older subjects (67.1 ± 1.2 yr mean±s.d.) received racemic, unlabeled **verapamil** orally for 16 days (120 mg twice daily). Rifampicin (600 mg daily) was coadministered from day 5 to 16. Using stable isotope technol. (i.e. i.v. coadministration of 10 mg deuterated **verapamil**) during **verapamil** steady-state without (day 4) and with rifampicin (day 16) bioavailability, prehepatic and hepatic extraction of **verapamil** were determined The effects of **verapamil** on AV-conduction were measured by the maximum PR interval prolongation (%). Bioavailability of the cardiovascularly more active S-**verapamil** decreased from 14.2±4.3% on day 4 to 0.6±0.5% on day 16 ($P<0.001$). As a consequence, effects of orally administered **verapamil** on the AV-conduction were nearly abolished (14.4±9.4% vs 2.7±2.6%, $P<0.01$). This could be attributed to a considerable increase of prehepatic extraction during treatment with rifampicin (41.7±22.1% vs 91.6±6.6%, $P<0.01$) and to a minor extent to induction of hepatic metabolism (73.7±9.4% vs 91.6±5.3%, $P<0.01$). Prehepatic metabolism of **verapamil** occurred in the group of older people investigated. Induction of gut wall metabolism most likely was the major reason for the loss of **verapamil** effect during treatment with rifampicin in this group of older subjects.

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 16 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:527240 CAPLUS
DOCUMENT NUMBER: 125:212096
TITLE: **Dexverapamil** to overcome epirubicin resistance in advanced breast **cancer**
AUTHOR(S): Thuerlimann, B.; Kroeger, N.; Greiner, J.; Mross, K.; Schueller, J.; Schernhammer, E.; Schumacher, K.; Gastl, G.; Hartlapp, J.; et al.
CORPORATE SOURCE: Department C Internal Medicine, Kantonsspital, St. Gallen, CH-9007, Switz.
SOURCE: Journal of Cancer Research and Clinical Oncology (1995), 121(Suppl. 3, Dexverapamil: A clinical approach to circumvention of multidrug resistance in cancer), R3-R6
CODEN: JCROD7; ISSN: 0171-5216
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The combination of oral **dexverapamil** (D), a 2nd-generation chemosensitizer currently in clin. development for multidrug resistance (MDR) reversal, with epirubicin (E) in patients with epirubicin-refractory high-risk metastatic breast **cancer** was investigated to evaluate feasibility and activity of the combination. Patients first received E alone at 120 mg/m2. In clin. refractoriness, E was continued at the same dose and schedule but supplemented with oral D. D was given at 300 mg every 6 h for a total of 13 doses and commenced 2 days prior to E administration. Addition of D resulted in a significant decrease in mean heart rate and blood pressure, and prolongation of PQ time as compared to E alone. These cardiovascular effects of D were usually mild, and subjective tolerance of treatment was good. In 7/14 patients, dose escalation of D was feasible. In 2/14 patients, the addition of D temporarily prevented further **tumor** progression. Addition of oral D to E 120/m2 proved to be feasible in a multiinstitutional setting.

L13 ANSWER 17 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:597876 CAPLUS
DOCUMENT NUMBER: 115:197876
TITLE: Reduction of multidrug resistance with (R)-**verapamil** in vitro and in vivo

AUTHOR(S): Pommerenke, E. W.; Mattern, J.; Traugott, U.; Volm, M.
CORPORATE SOURCE: Inst. Exp. Pathol., Dtsch. Krebsforschungszent., Heidelberg, W-6900, Germany
SOURCE: Arzneimittel-Forschung (1991), 41(8), 855-8
CODEN: ARZNAD; ISSN: 0004-4172
DOCUMENT TYPE: Journal
LANGUAGE: German
AB (R)-**Verapamil** and (RS)-**verapamil** equally decreased the resistance to doxorubicin of doxorubicin-resistant L1210 ascites **tumor** cells in vitro and in mice, indicating modification of multidrug resistance. However, the R-isomer caused fewer symptoms of host toxicity than did the racemate. Neither (R)- nor (RS)-**verapamil** altered the cytotoxicity of doxorubicin to doxorubicin-sensitive **tumor** cells nor the resistance to ara C in ara C-resistant **tumor** cells.

L13 ANSWER 18 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:578080 CAPLUS
DOCUMENT NUMBER: 132:117093
TITLE: The effect of ketoconazole on the jejunal permeability and CYP3A metabolism of (R/S)-**verapamil** in humans
AUTHOR(S): Sandstrom, Rikard; Knutson, Tina W.; Knutson, Lars; Jansson, Britt; Lennernas, Hans
CORPORATE SOURCE: Department of Pharmacy, Uppsala University, Uppsala, S-751 23, Swed.
SOURCE: British Journal of Clinical Pharmacology (1999), 48(2), 180-189
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This human intestinal perfusion study investigated the effect of ketoconazole on the jejunal permeability and 1st-pass metabolism of (R)- and (S)-**verapamil** in humans. A regional single-pass perfusion of the jejunum was performed in healthy volunteers. Each perfusion lasted 200 min and was divided into 2 periods of 100 min each. The infusion concentration of (R/S)-**verapamil** was 120 mg/L in both periods, and ketoconazole was added at 40 mg/L in period 2. (R/S)-**verapamil** was also administered as a short i.v. infusion of 5 mg, over a period of 10 min. The ratios of the cytochrome P 450 3A (CYP3A)-formed metabolites (R)- and (S)-norverapamil were also determined in the outlet jejunal perfusate. The effective jejunal permeability of both (R)- and (S)-**verapamil** was unaffected by the addition of ketoconazole in period 2, suggesting that ketoconazole had no effect on the P-glycoprotein-mediated efflux. However, the appearance of both (R)- and (S)-norverapamil in the outlet jejunal perfusate decreased in the presence of ketoconazole. The rate of absorption (R)- and (S)-**verapamil** into plasma increased despite the low dose of ketoconazole added, indicating an inhibition of the gut wall metabolism of (R/S)-**verapamil** by ketoconazole. Thus, ketoconazole did not affect the jejunal effective jejunal permeability of (R/S)-**verapamil**, but it did increase the overall transport into the systemic circulation (bioavailability), probably by inhibition of the gut wall metabolism of **verapamil**. This might be due to ketoconazole being less potent as an inhibitor of P-glycoprotein than of CYP3A4 in vivo in humans.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 19 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:141145 CAPLUS
DOCUMENT NUMBER: 140:296807
TITLE: Prediction of cytochrome P450 3A inhibition by **verapamil** enantiomers and their metabolites

AUTHOR(S): Wang, Ying-Hong; Jones, David R.; Hall, Stephen D.
CORPORATE SOURCE: Division of Clinical Pharmacology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA
SOURCE: Drug Metabolism and Disposition (2004), 32(2), 259-266
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Verapamil** inhibition of CYP3A activity results in many drug-drug interactions with CYP3A substrates, but the mechanism of inhibition is unclear. The present study showed that **verapamil** enantiomers and their major metabolites [norverapamil and N-desalkylverapamil (D617)] inhibited CYP3A in a time- and concentration-dependent manner by using pooled human liver microsomes and the cDNA-expressed CYP3A4 (+b5). The values of the inactivation kinetic parameters kinact and Kl obtained with the cDNA-expressed CYP3A4 (+b5) were 0.39 min-1 and 6.46 μM for R-**verapamil**, 0.64 min-1 and 2.97 μM for S- **verapamil**, 1.12 min-1 and 5.89 μM for (±)-norverapamil, and 0.07 min-1 and 7.93 μM for D617. Based on the ratio of kinact and Kl, the inactivation potency of **verapamil** enantiomers and their metabolites was in the following order: S-norverapamil > S-**verapamil** > R-norverapamil > R-**verapamil** > D617. Using dual beam spectrophotometry, we confirmed that metabolic intermediate complex formation with CYP3A was the mechanism of inactivation for all compds. The in vitro unbound fraction was 0.84 for S-**verapamil**, 0.68 for R-**verapamil**, and 0.84 for (±)-norverapamil. A mechanism-based pharmacokinetic model predicted that the oral area under the curve (AUC) of a CYP3A substrate that is eliminated completely (fm = 1) by the hepatic CYP3A increased 1.6- to 2.2-fold after repeated oral administration of **verapamil**. For midazolam (fm = 0.9), a drug that undergoes extensive intestinal wall metabolism, the predicted increase in oral AUC was 3.2- to 4.5-fold. The predicted results correlate well with the in vivo drug interaction data, suggesting that the model is suitable for predicting drug interactions by mechanism-based inhibitors.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 20 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:391637 CAPLUS
DOCUMENT NUMBER: 129:117396
TITLE: Jejunal absorption and metabolism of R/S-**verapamil** in humans
AUTHOR(S): Sandstrom, Rikard; Karlsson, Anders; Knutson, Lars; Lennernas, Hans
CORPORATE SOURCE: Department of Pharmacy, Biomedical Centre, University of Uppsala, Uppsala, S-751 23, Swed.
SOURCE: Pharmaceutical Research (1998), 15(6), 856-862
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Plenum Publishing Corp.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The transport and metabolism of R/S-**verapamil** were studied in the human jejunum perfusion study in vivo. A regional single-pass perfusion of the jejunum was performed using a Loc-I-Gut perfusion tube in 12 healthy volunteers. Each perfusion lasted for 200 min and was divided into 2 periods each of 100 min. The inlet concns. of **verapamil** were 4.0 and 40 mg/L in period 1 and 2, resp. The effective jejunal permeability (Peff) of both R- and S-**verapamil** increased when the inlet concentration was increased, consistent with the saturation of an efflux mechanism. However, both R- and S-**verapamil** had high intestinal Peff, consistent with a complete absorption. The Peff of antipyrine also

increased, but there was no difference in the Peff for D-glucose in the 2 periods. The appearance of R/S-norverapamil in the intestinal perfusate leaving the jejunal segment was nonlinear, presumably due to saturation of the cytochrome P 450 3A4 metabolism The increased Peff in parallel with the increased entering drug concentration is most likely due to saturable efflux by P-glycoprotein(s) in the human **intestine**.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 21 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:918823 CAPLUS
DOCUMENT NUMBER: 124:75525
TITLE: Structure-activity relationship of **verapamil** analogs and reversal of multidrug resistance
AUTHOR(S): Toffoli, G.; Simone, F.; Corona, G.; Raschack, M.; Capelletto, B.; Gigante, M.; Boiocchi, M.
CORPORATE SOURCE: Div. of Experimental Oncology 1, Centro diRiferimento Oncologico, Aviano, 33081, Italy
SOURCE: Biochemical Pharmacology (1995), 50(8), 1245-55
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We studied the relationship between the chemical structure and multidrug resistance (MDR) reversal activity of racemic **verapamil** (VER) and 14 VER analogs (VAs). The LoVo-R human colon carcinoma cell line was used as an exptl. model. This cell line exhibited a typical MDR phenotype and overexpressed the MDR1 gene products. Key structural features were identified as being related to MDR reversal and cytotoxic activity. In particular, we demonstrated that the methoxy groups in the VER mol. structure [1,7-Bis-(3,4-dimethoxyphenyl)-3-methylaza-7-cyano-8-methylnonane] prevented cytotoxicity when the VAs were used alone, whereas the 7-cyano-8-Me groups were important for MDR reversal activity and interaction with P-glycoprotein (P-gp). Among the VAs tested. the most active compds. were gallopamil, R-isomer of VER (R-VER), and nor-VER, which potentiated doxorubicin (DOX) cytotoxicity by 52.3±7.2 (n=3±SD), 38.9±6.4 (n=4±SD), and 35.4±4.3 (n=3±SD) times, resp. The reversal activity of these compds. was similar to that of VER, which enhanced DOX cytotoxicity by 41.3±5.0 (n=3±SD) times. The potentiation of DOX cytotoxicity was associated with an increase in DOX uptake in LoVo-R cells and with an increased [3H]azidopine P-gp photolabeling inhibition. Some compds. that had a high reversal potency (i.e. R-VER and nor-VER) showed a lower calcium antagonist activity than VER, and seem useful candidates for the treatment of MDR in **cancer** patients.

L13 ANSWER 22 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:548839 CAPLUS
DOCUMENT NUMBER: 127:214774
TITLE: Treatment of advanced colorectal **cancer** with doxorubicin combined with two potential multidrug-resistance-reversing agents. High-dose oral tamoxifen and **dexverapamil**
AUTHOR(S): Weinlander, G.; Kornek, G.; Raderer, M.; Hejna, M.; Tetzner, C.; Scheithauer, W.
CORPORATE SOURCE: Medical School, University Vienna, Vienna, A-1090, Austria
SOURCE: Journal of Cancer Research and Clinical Oncology (1997), 123(8), 452-455
CODEN: JCROD7; ISSN: 0171-5216
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB On the basis of the overexpression of the MDR1 gene in human colorectal

cancer, which may constitute a mol. basis for intrinsic drug resistance that can be reversed, and because of the limited therapeutic value of conventional cytotoxic treatment in this disease, the present phase II study of P-glycoprotein-directed double modulation was initiated. Fifteen patients with measurable metastatic colorectal **cancer**, all of whom were refractory to 1st-line chemotherapy with 5-fluorouracil/leukovorin, were entered in this trial. Treatment consisted of 80 mg tamoxifen twice daily on days 1-9, oral **dexverapamil** every day on days 7-9, and 60 mg/m2 doxorubicin given by i.v. bolus injection on day 8. Courses were repeated every 4 wk. After a median of 3 courses, none of the 14 evaluable patients had objective response, and 4 had stable disease. Adverse reactions consisted mainly of myelosuppression (WHO grade IV granulocytopenia was noted in 40%), and mild and reversible **dexverapamil**-related cardiovascular side-effects, specifically hypotension (47%). Thus, despite the histol. demonstration of high levels of P-glycoprotein in colorectal **cancer** and administration of 2 potentially synergistic chemosensitizers, the authors were unsuccessful in circumventing its primary resistance to chemotherapy.

L13 ANSWER 23 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:112223 CAPLUS
DOCUMENT NUMBER: 128:162882
TITLE: Therapeutic utilities of **verapamil** enantiomers
INVENTOR(S): Harding, Deborah Phyllis; Greaves, Jane Lizbeth
PATENT ASSIGNEE(S): Chiroscience Ltd., UK; Harding, Deborah Phyllis; Greaves, Jane Lizbeth
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9805321	A1	19980212	WO 1997-GB2094	19970806
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9737784	A1	19980225	AU 1997-37784	19970806
ZA 9707005	A	19980806	ZA 1997-7005	19970806
EP 925062	A1	19990630	EP 1997-934642	19970806
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
US 5932246	A	19990803	US 1997-907151	19970806
JP 2000515539	T2	20001121	JP 1998-507726	19970806

PRIORITY APPLN. INFO.: GB 1996-16504 A 19960806
GB 1996-16550 A 19960806
WO 1997-GB2094 W 19970806

AB A substantially single enantiomer of R- or S-**verapamil**, or a pharmaceutically-acceptable salt thereof, provides an improved treatment for patients having a condition susceptible to treatment with racemic **verapamil** and who are disposed to constipation. In a gastrointestinal transit study with volunteers, results showed that racemic **verapamil** had a significant constipating effect on large bowel transit. No significant differences in large bowel transit were observed for either of the individual **verapamil** enantiomers or the placebo control.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 24 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:376402 CAPLUS
DOCUMENT NUMBER: 138:348722
TITLE: Treatment of abnormal increases in gastrointestinal motility with (R)-**verapamil**
INVENTOR(S): Kelly, John; Devane, John
PATENT ASSIGNEE(S): Ire.
SOURCE: U.S. Pat. Appl. Publ., 19 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003092765	A1	20030515	US 2002-256261	20020927
US 2004063784	A1	20040401	US 2002-294692	20021115
WO 2004032919	A1	20040422	WO 2002-IB5140	20021115

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-335959P P 20011115
US 2002-256261 B2 20020927

AB The present invention is directed to methods of treating, preventing, and/or managing abnormal increases in gastrointestinal motility, and intestinal conditions that cause the same. Such conditions include, but are not limited to, irritable bowel syndrome (IBS), infectious diseases of the small and large **intestines**, and symptoms of any of the foregoing. In particular, the present invention discloses methods of using (R)-**verapamil**, as well as compns. and formulations containing the same.

L13 ANSWER 25 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:89573 CAPLUS
DOCUMENT NUMBER: 128:136116
TITLE: Modulation of vincristine cytotoxicity by **dexverapamil** in sensitive and resistant HL-60 cell lines as a function of extracellular protein binding
AUTHOR(S): Stratmann, G.; Harder, S.; Hoelzer, D.; Hoffmann, W. K.; Ottmann, O. G.; Woodcock, B. G.
CORPORATE SOURCE: Inst. Clinical Pharmacology, JWG-Univ., Frankfurt/Main, D-60590, Germany
SOURCE: International Journal of Clinical Pharmacology and Therapeutics (1998), 36(2), 103-106
CODEN: ICTHEK; ISSN: 0946-1965
PUBLISHER: Dustri-Verlag Dr. Karl Feistle
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In view of multidrug resistance **dexverapamil** was studied as chemosensitizer in the sensitive HL-60 and the resistant Hl-60-vinc cell lines with RPMI/15% FCS and human serum in the presence of AGP, reflecting

elevated levels in **cancer**. The effect of **dexverapamil** on the protein binding of vincristine, the influence of different protein solns. on vincristine accumulation and cytotoxicity, and the chemosensitizing effect of **dexverapamil** was examined Vincristine binding was 2-fold higher in human serum than in RPMI/FCS, the difference being increased in the presence of **dexverapamil**. Differences in vincristine accumulation in the absence of **dexverapamil** were only moderate indicating that the reduced chemosensitizing effect of human serum and in presence of AGP depends on the high **dexverapamil** binding. **Dexverapamil** increased vincristine accumulation in both cell lines in RPMI/FCS indicating that other **verapamil** -sensitive mechanisms are involved in HL-60 cells. The authors suggest that the chemosensitizing potency of **dexverapamil** is substantially reduced in human serum and in the presence of AGP.

L13 ANSWER 26 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:494365 CAPLUS
DOCUMENT NUMBER: 131:252059
TITLE: Repeated oral rifampicin decreases the jejunal permeability of R/S-**verapamil** in rats
AUTHOR(S): Sandstrom, Rikard; Lennernas, Hans
CORPORATE SOURCE: Department of Pharmacy, Uppsala University, Uppsala, S-751 23, Swed.
SOURCE: Drug Metabolism and Disposition (1999), 27(8), 951-955
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The main purpose of this rat study was to investigate the effect of rifampicin on the effective permeability (Peff) of R/S-**verapamil** in the rat jejunum. In addition the effect on metabolism of R/S-**verapamil** to R/S-norverapamil was examined In situ single-pass perfusions of the rat jejunum were performed in animals pretreated with oral rifampicin (250 mg/kg/day) or saline (control) over various time periods (1, 4, 7, and 14 days). The jejunal Peff of each of the enantiomers of **verapamil** and D-glucose was estimated The appearance ratios of the CYP3A-formed metabolites R- and S-norverapamil were also estimated in the outlet jejunal perfusate. The jejunal Peff of both R- and S-**verapamil** decreased as an effect of the oral pretreatment with rifampicin. The appearance of R- and S-norverapamil in the jejunum was also affected by the oral pretreatment with rifampicin, with increasing concns. of R/S-norverapamil being evident after 14 days of rifampicin pretreatment. There was no stereoselectivity in either the Peff of R- and S-**verapamil** or the metabolic appearance of R- and S-norverapamil. Treatment with oral rifampicin decreased the Peff of R/S-**verapamil**, which is in accordance with an induction of P-glycoprotein activity in the apical enterocyte membrane. The increase in appearance of R/S-norverapamil in jejunum is in accordance with an induction of CYP3A metabolism in the rat.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 27 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:977175 CAPLUS
DOCUMENT NUMBER: 140:280930
TITLE: **Verapamil** regulates activity and mRNA-expression of human β-glucuronidase in HepG2 cells
AUTHOR(S): Grube, M.; Kunert-Keil, C.; Sperker, B.; Kroemer, H. K.
CORPORATE SOURCE: Department of Pharmacology, Peter Holtz Research Center of Pharmacology and Experimental Therapeutics, Friedrich Loefflerstrasse 23d, Greifswald, 17487,

Germany
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (2003), 368(6), 463-469
CODEN: NSAPCC; ISSN: 0028-1298
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A promising development in **tumor** therapy is the application of non-toxic prodrugs from which the active cytostatic is released by endogenous enzymes such as β-glucuronidase (β-gluc). Regulation of β-gluc expression is one crucial factor modulating bioactivation of prodrugs. Recent expts. in rats indicate regulation of β-gluc activity by the calcium channel blocker **verapamil**. To further explore this phenomenon, we investigated the effect of **verapamil** on β-gluc enzyme activity, protein (western blot) and mRNA expression (RT-PCR) as well as the underlying mechanisms (effects of **verapamil** metabolites; promoter activity) in the human hepatoma cell line HepG2. Treatment of HepG2 cells with **verapamil** revealed down-regulation of β-gluc activity, protein, and mRNA level down to 50% of the control with EC50 values of 25 μM. Effects were similar for both enantiomers. Moreover, it was demonstrated that reduced promoter activity contributes to the observed effects. In summary, our data demonstrate regulation of human β-glucuronidase expression by **verapamil**. Based on our findings we hypothesize that coadministration of **verapamil** may effect cleavage of glucuronides by β-glucuronidase.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 28 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:564960 CAPLUS
DOCUMENT NUMBER: 113:164960
TITLE: Human multidrug-resistant **cancer** cells exhibit a high degree of selectivity for stereoisomers of **verapamil** and quinidine
AUTHOR(S): Eliason, James F.; Ramuz, Henri; Kaufmann, Franz
CORPORATE SOURCE: Dep. Exp. Dermatol./Oncol., F. Hoffmann-La Roche Ltd., Basel, CH-4002, Switz.
SOURCE: International Journal of Cancer (1990), 46(1), 113-17
CODEN: IJCNAW; ISSN: 0020-7136
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An in vitro cell proliferation assay with MTT was developed to measure the capacity of substances to overcome multidrug resistance (MDR). The inclusion of cell titration curves for each concentration of the resistance modifier (RM) allows the IC50 of the RM to be calculated and provides empirical correction of the cell survival curves for the effect of the RM when it is combined with a standard cytotoxic drug, vincristine. The resistance modification index (RMI) is defined as the ratio of the IC50 of vincristine obtained in control cultures divided by that measured in the presence of RM and is linearly related to the dose of RM. The RMI0.1 (RMI a a 1/10 of the IC50 of the RM) provides a relative comparison between the activities of different RMs at non-toxic doses. The results obtained using the MDR cell line KB-8-5 show that l-(-)-**verapamil** is .apprx.4 times more active than d-(+)-**verapamil** in modifying MDR. The racemic mixture has an intermediate activity. A similar comparison between the epimers quinidine and quinine shows that, at equimolar doses, quinine has a higher RMI but, because it is more toxic, the RMI0.1 is about one-half of that of quinidine. These results demonstrate the importance of comparing the resistance-modifying activities of different compds. at doses relative to their own toxicity.

L13 ANSWER 29 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1988:637028 CAPLUS
DOCUMENT NUMBER: 109:237028
TITLE: Pharmaceuticals containing phenylacetonitrile calcium antagonists for the prevention of **tumor** metastasis
INVENTOR(S): Daum, Lothar; Emling, Franz; Keilhauer, Gerhard; Seitz, Werner
PATENT ASSIGNEE(S): BASF A.-G., Fed. Rep. Ger.
SOURCE: Ger. Offen., 2 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3635931	A1	19880428	DE 1986-3635931	19861022
JP 63264414	A2	19881101	JP 1987-262940	19871020
AU 8779996	A1	19880428	AU 1987-79996	19871021
AU 607941	B2	19910321		
EP 270782	A2	19880615	EP 1987-115378	19871021
EP 270782	A3	19900103		
EP 270782	B1	19920812		
R: AT, BE, CH, DE, ES, FR, GB, IT, LI, NL, SE				
ZA 8707900	A	19890628	ZA 1987-7900	19871021
AT 79255	E	19920815	AT 1987-115378	19871021
ES 2051721	T3	19940701	ES 1987-115378	19871021

PRIORITY APPLN. INFO.: DE 1986-3635931 19861022
EP 1987-115378 19871021

AB (+)-**Verapamil** (I), (+)-gallopamil, (+)-devapamil, or (+)-emopamil are used for the prevention of **tumor** metastasis. Tablets contained I 500, lactose 120, cellulose 60, Mg stearate 3, corn starch 50, and poly(vinylpyrrolidone) 15 mg esch.

L13 ANSWER 30 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:515223 CAPLUS
DOCUMENT NUMBER: 129:225392
TITLE: The absence of stereoselective P-glycoprotein-mediated transport of R/S-**verapamil** across the rat jejunum
AUTHOR(S): Sandstrom, Rikard; Karlsson, Anders; Lennernas, Hans
CORPORATE SOURCE: Department of Pharmacy, Division of Biopharmaceutics and Pharmacokinetics, University of Uppsala, Uppsala, S-75123, Swed.
SOURCE: Journal of Pharmacy and Pharmacology (1998), 50(7), 729-735
CODEN: JPPMAB; ISSN: 0022-3573
PUBLISHER: Royal Pharmaceutical Society of Great Britain
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have studied the potential stereoselective transport and metabolism of R/S-**verapamil** in rat jejunum, in-situ. A regional single-pass perfusion of the rat jejunum was performed on 24 rats in six sep. groups. The effective permeability (Peff) was assessed for three different concns. of **verapamil**, 4, 40 and 400 mg L-1. The Peff of each enantiomer was also determined at 400 mg L-1 when chlorpromazine (10 mM) was added to the perfusion solution Two other groups of rats received R/S-**verapamil** as an i.v. infusion and the intestinal secretion and metabolism were studied by simultaneously perfusing the jejunum with a control or with chlorpromazine (10 mM) added. The concns. in the outlet perfusate of each enantiomer of **verapamil** and norverapamil were assayed with HPLC. R/S-**verapamil** is a high permeability drug in the proximal rat small **intestine** throughout the luminal concentration

range studied and complete intestinal absorption was expected. There was an increase of Peff from 0.42+10-4 cm s-1 to 0.80+10-4 cm s-1 at concns. from 4 to 400 mg L-1, resp. The observed concentration-dependent jejunal Peff and fraction absorbed of R/S-**verapamil** is consistent with the saturation of an efflux mechanism. When chlorpromazine (a P-glycoprotein inhibitor/substrate) was added the jejunal Peff increased to 1.47+10-4 cm s-1. There was no difference between the Peff of the two enantiomers in any of these expts. The efflux of R/S-norverapamil into the rat jejunum was high after i.v. administration of R/S-**verapamil**, suggesting extensive metabolism in the enterocyte. In conclusion, both R/S-**verapamil** enantiomers are P-glycoprotein substrates, but there is no stereoselective transport of R/S-**verapamil** in the rat jejunum. The results also suggests that R/S-norverapamil is formed inside the enterocytes.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 31 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:616891 CAPLUS
DOCUMENT NUMBER: 119:216891
TITLE: R-**verapamil**: pharmacokinetics and effects on PR interval, blood pressure and heart rate
AUTHOR(S): Ahmed, J. H.; Godden, J.; Meredith, P. A.; Elliott, H. L.
CORPORATE SOURCE: Gardiner Inst., West. Infirm., Glasgow, G11 6NT, UK
SOURCE: British Journal of Clinical Pharmacology (1993), 36(2), 93-8
CODEN: BCPHBM; ISSN: 0306-5251
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study in healthy normotensive male volunteers investigated the pharmacokinetics and the effects on electrocardiog. PR interval, blood pressure and heart rate of single oral doses of the single isomer R-**verapamil** (250, 500 and 1000 mg) in comparison to placebo and 240 mg racemic **verapamil**. After 500 and 1000 mg R-**verapamil** , there were significant prolongations in PR interval, maximal at 1-2 h after dosing and coincident with peak plasma drug concns., but these were not significantly different from the maximum prolongation obtained with 240 mg racemic **verapamil**. After 1000 mg R-**verapamil**, there was a significant hypotensive effect, particularly on standing. Single doses of 500 and 1000 mg R-**verapamil** produced peak plasma drug concns. in the range 1000-3000 ng mL-1. If this concentration range is appropriate for adjuvant **cancer** chemotherapy, it can be predicted that similar steady state concns. will occur with a dosage regimen of 300 mg 3 times daily.

L13 ANSWER 32 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:736788 CAPLUS
DOCUMENT NUMBER: 123:132272
TITLE: Controlled trial of **dexverapamil**, a modulator of multidrug resistance, in lymphomas refractory to EPOCH chemotherapy
AUTHOR(S): Wilson, Wyndham H.; Bates, Susan E.; Fojo, Antonio; Bryant, George; Zhan, Zhirong; Regis, JoAnna; Wittes, Robert E.; Jaffe, Elaine S.; Steinberg, Seth M.; et al.
CORPORATE SOURCE: Medicine Branch, National Cancer Inst., Bethesda, MD, USA
SOURCE: Journal of Clinical Oncology (1995), 13(8), 1995-2004
CODEN: JCONDN; ISSN: 0732-183X
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Overexpression of the multidrug resistance gene (mdr-1) is present in up to 0% of relapsed lymphomas. To study its role in lymphomas, we conducted a controlled trial of **dexverapamil**, an inhibitor of the mdr-1 gene product, P-glycoprotein (Pgp), in lymphomas refractory to etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) chemotherapy. Eligible patients had recurrent Hodgkin's (HD) or non-Hodgkin's lymphomas (NHL) and measurable disease. Patients initially received EPOCH alone and those with stable **tumor** over 2 cycles or progressive disease crossed over to receive **dexverapamil** and EPOCH on subsequent cycles. **Dexverapamil** was escalated 8 dose levels, from 240 to 1200 mg/m2/d. When possible, serial biopsies were obtained to measure mdr-1 expression by quant. polymerase chain reaction (PCR). Of 154 patients entered onto the trial, 109 had NHL and 45 had HD. The median age was 44 yr, 67% had stage IV disease, and the median number of prior regimens was two (range, one to 12) in NHL and one (range, one to four) in HD. Sixty-four patients (42%) crossed over, of which 8 were not accessable. The maximum-tolerated dose of **dexverapamil** was 900 mg/m2/d. Among 41 NHL patients (excluding mycosis fungoides), there were 3 complete responses (CRs) and two partial responses (PRs) (12%) and 5 minor responses (MRs); 2 of 10 HD patients achieved PRs. The mdr-1 level was measured in 44 biopsies from 19 patients. Pretherapy, mdr-1 was low (median, 2.5 U) but increased (median, 12.2 U) at crossover. Of six patients with mdr-1 levels greater than 15 U, 3 responded to **dexverapamil**, while only 1 of 8 patients with mdr-1 levels less than 15 U responded. EPOCH and **dexverapamil** were well tolerated, but compared with EPOCH alone, produced more hematol. toxicity. These results suggest that Pgp plays a role in clin. drug resistance of lymphomas. However, they also suggest that mechanisms other than Pgp are prominent in heavily pretreated patients and that, although Pgp inhibition may be necessary, it is probably insufficient. Earlier intervention with **dexverapamil** may be more effective and warrants further study.

L13 ANSWER 33 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:262000 CAPLUS
DOCUMENT NUMBER: 127:44582
TITLE: In vitro effects of R-**verapamil** on the cytokine environment and T-lymphocyte proliferation when human T-lymphocyte activation takes place in the presence of acute myelogenous leukemia blasts
AUTHOR(S): Bruserud, Oystein
CORPORATE SOURCE: Haukeland Hospital, University Bergen, Bergen, N-5021, Norway
SOURCE: Cancer Chemotherapy and Pharmacology (1996), 39(1/2), 71-78
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Interleukin 4 (IL4) and interferon-γ (IFNγ) release was inhibited by R-**verapamil** from polyclonal T-cells activated with T-cell mitogen phytohemagglutinin, and proliferation and release of IFNγ and IL10 by normal T-cells stimulated with allogeneic peripheral blood mononuclear cells derived from acute myelogenous leukemia patients. The antiproliferative effect was in the presence of exogenous IL2. R-**verapamil** inhibited the release of IL1β and TNF-α during allogeneic stimulation.

L13 ANSWER 34 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:390046 CAPLUS
DOCUMENT NUMBER: 125:75602
TITLE: Cellular drug efflux and reversal therapy of **cancer**
AUTHOR(S): Wigler, Paul W.
CORPORATE SOURCE: Dep. Med. Biol., Univ. Tennessee Med. Cent.,

Knoxville, TN, 37920, USA
SOURCE: Journal of Bioenergetics and Biomembranes (1996), 28(3), 279-284
CODEN: JBBID4; ISSN: 0145-479X
PUBLISHER: Plenum
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A prevalent form of multidrug resistance (MDR) in **cancer** cells is caused by an ATP-dependent drug efflux pump; this pump catalyzes the rapid exit of cytotoxic chemotherapy drugs from the cells. The Michaelis equation can be used to describe drug efflux through the MDR pump at a low drug substrate concentration [S]. The inhibition mechanism of an MDR reversal agent can be characterized when two different values of [S] are used to determine two values for the half-inhibition of efflux through the pump (I50) are identical; the reaction is competitive when an increase in [S] produces a significant increase in the value of I50. The I50 has been determined for several different reversal agents with the substrate rhodamine 123. The inhibition potency observed is: cyclosporin A > DMDP > amiodarone > **verapamil** > quinidine > quinine > propranolol. Chemotherapy drugs that are potent inhibitors of the MDR pump could be used for the treatment of MDR neoplasia.

L13 ANSWER 35 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:595238 CAPLUS
DOCUMENT NUMBER: 119:195238
TITLE: Effects of dipyridamole and R-**verapamil** on in vitro proliferation of blast cells from patients with acute myelogenous leukemia
AUTHOR(S): Bruserud, Oeystein; Pawelec, Graham
CORPORATE SOURCE: Med. Dep. B., Haukeland Univ. Hosp., Bergen, N-5021, Norway
SOURCE: Leukemia Research (1993), 17(6), 507-13
CODEN: LEREDD; ISSN: 0145-2126
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cytokine-dependent AML cell proliferation was investigated in 16 patients. Dipyridamole and R-**verapamil** caused a dose-dependent inhibition of AML cell proliferation, and for both drugs the degree of inhibition was similar when testing various hematopoietic growth factors or growth factor combinations (IL3, G-CSF, GM-CSF, G-CSF, G-CSF + CM-CSF, TNF-α+ GM-CSF). TNFα alone increased AML cell proliferation for five patients, whereas four patients showed unaltered or decreased proliferation. Independent of this TNF-α effect, R-**verapamil** inhibited proliferation for all AML patients in the presence of TNF-α, whereas dipyridine caused only a weak inhibition.

L13 ANSWER 36 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:305783 CAPLUS
DOCUMENT NUMBER: 125:48521
TITLE: P-glycoprotein-associated resistance to taxol and taxotere and its reversal by dexniguldipine-HCl, **dexverapamil**-HCl, or cyclosporin A
AUTHOR(S): Ise, Wolfgang; Heuser, Margrit; Sanders, Karl Heinrich; Beck, James; Gekeler, Volker
CORPORATE SOURCE: Byk Gulden GmbH, Konstanz, D-78403, Germany
SOURCE: International Journal of Oncology (1996), 8(5), 951-956
CODEN: IJONES; ISSN: 1019-6439
PUBLISHER: International Journal of Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of different human MDR (multidrug-resistant) cell lines including a HeLa-MDR1 transfectant which exhibit high overexpression of the MDR1/P-glycoprotein gene, but no enhanced expression of the MRP (multidrug

resistance associated protein) gene, showed different ratios of relative resistances to the taxanes taxol and taxotere. Using these cell lines the chemosensitizing efficacies of several structurally different chemosensitizers, i.e. the dihydropyridine dexniguldipine-HCl (B8509-035), its main pyridine metabolite M1 (B8909-008), the cyclic peptide cyclosporin A, or the phenylalkylamine **dexverapamil**-HCl, were examined applying a 72 h tetrazolium based colorimetric MTT-assay, or a 96 h sulforhodamine B assay. Remarkably, we observed in some instances that the modulating efficacy of a particular chemosensitizer was strongly dependent on the cell line used for experimentation. Thus, dexniguldipine-HCl efficiently modulated taxane resistances of the ovarian carcinoma MDR cell line 2780AD in the submicromolar concentration range, whereas cyclosporin A and the other chemosensitizers were rather ineffective. Dexniguldipine-HCl or cyclosporin A, however, both showed a similarly strong modulating activity on the HeLa-MDR1 transfectant in clear contrast to the effects observed using the pyridine B8909-008, or **dexverapamil**-HCl, resp., at the same final concns. Our results point to addnl., as yet unidentified factors beyond the expression levels of P-glycoprotein which could contribute to the susceptibility of MDR cells to a combined treatment using taxanes and different chemosensitizing compds. This result appears to be important considering the clin. application of chemosensitizers for combination therapy of **tumors** of different origin.

L13 ANSWER 37 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:569646 CAPLUS
DOCUMENT NUMBER: 121:169646
TITLE: Inhibition of P-glycoprotein-mediated vinblastine transport across HCT-8 intestinal carcinoma monolayers by **verapamil**, cyclosporine A and SDZ PSC 833 in dependence on extracellular pH
AUTHOR(S): Zacherl, Johannes; Hamilton, Gerhard; Thalhammer, Therese; Riegler, Martin; Cosentini, Enrico P.; Ellinger, Adolf; Bischof, Georg; Schweitzer, Michael; Teleky, Bela; et al.
CORPORATE SOURCE: Department Surgery, University Vienna, Vienna, A-1090, Austria
SOURCE: Cancer Chemotherapy and Pharmacology (1994), 34(2), 125-32
CODEN: CCPHDZ; ISSN: 0344-5704
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The ability of the multidrug resistance modifiers R- and R,S-**verapamil** (VPL), cyclosporine A (CsA) and its non-immunosuppressive derivative SDZ PSC 833 (PSC 833) to inhibit P-glycoprotein (P-gp)-mediated transepithelial flux of tritiated vinblastine was investigated using tight and highly resistant (R > 1,400 Ω cm2) monolayer cultures of intestinal adenocarcinoma-derived HCT-8 cells grown on permeable tissue-culture inserts. Apical addition of these chemosensitizers inhibited drug flux (137 pmol h-1 cm-2; range, 133-142 pmol h-1 cm-2) in the basal to apical secretory direction at clin. relevant concns., with PSC 833 showing the highest activity, exhibiting inhibition at concns. as low as 10 ng/mL (9 nM). Acidification of the modulator-containing apical compartment to an extracellular pH (pHo) of 6.8 had no influence on MDR reversal by CsA at 1 μg/mL (0.9 μM; flux inhibition, 52%) or by PSC 833 at 100 ng/mL (0.09 μM; flux inhibition, 60%), in contrast to R,S- and R-VPL, which showed decreased inhibition and caused less accumulation of vinblastine in HCT-8 cells under this condition (flux inhibition of 35% and 23%, resp., at pHo 6.8 vs 50% and 43%, resp., at pHo 7.5). P-gp-mediated rhodamine 123 efflux from dye-loaded single-cell suspensions of HCT-8 cells as measured by flow cytometry was not impeded at pHo 6.8 in comparison with pHo 7.5 in standard medium, but at low pHo the inhibitory activity of R-VPL (29% vs 60% rhodamine 123 efflux inhibition) was diminished significantly, again without a reduction in the effect of PSC 833 (rhodamine 123 flux inhibition,

75%). In conclusion, drug extrusion across polarized monolayers, which offer a relevant model for normal epithelia and **tumor** border areas, is inhibited by the apical presence of R,S- and R-VPL, CsA and PSC 833 at similar concns. described for single-cell suspensions, resulting in increased (2.2- to 3.7-fold) intracellular drug accumulation. Functional apical P-gp expression, the absence of paracellular leakage and modulator-sensitive rhodamine 123 efflux in single HCT-8 cells indicate a P-gp-mediated transcellular efflux in HCT-8 monolayers. In addition to its high MDR-reversing capacity, the inhibitory activity of PSC 833 is not affected by acidic extracellular conditions, which reduce the VPL-induced drug retention significantly. As far as MDR contributes to the overall cellular drug resistance of solid **tumors** with hypoxic and acidic microenvironments, PSC 833 holds the greatest promise for clin. reversal of unresponsiveness to the resp. group of chemotherapeutics.

L13 ANSWER 38 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:521462 CAPLUS
DOCUMENT NUMBER: 137:88442
TITLE: Incensole and furanogermacrens and compounds in treatment for inhibiting neoplastic lesions and microorganisms
INVENTOR(S): Shanahan-Pendergast, Elisabeth
PATENT ASSIGNEE(S): Ire.
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053138	A2	20020711	WO 2002-IE1	20020102
WO 2002053138	A3	20020919		
W: AE, AG, AT, AU, BB, BG, CA, CH, CN, CO, CU, CZ, LU, LV, MA, MD, UA, UG, US, VN, YU, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, AT, BE, CH, CY, DE, ES, FI, ML, MR, NE, SN, TD, TG				
EP 1351678	A2	20031015	EP 2002-727007	20020102
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004092583	A1	20040513	US 2004-250535	20040102

PRIORITY APPLN. INFO.: IE 2001-2 A 20010102
WO 2002-IE1 W 20020102
OTHER SOURCE(S): MARPAT 137:88442
AB The invention discloses the use of incensole and/or furanogermacrens, derivs. metabolites and precursors thereof in the treatment of neoplasia, particularly resistant neoplasia and immundysregulatory disorders. These compds. can be administered alone or in combination with conventional chemotherapeutic, antiviral, antiparasite agents, radiation and/or surgery. Incensole and furanogermacren and their mixture showed antitumor activity against various human carcinomas and melanomas and antimicrobial activity against Staphylococcus aureus and Enterococcus faecalis.

L13 ANSWER 39 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:955570 CAPLUS
DOCUMENT NUMBER: 124:75746
TITLE: Phase I/II trial of **dexverapamil**, epirubicin, and granulocyte-macrophage-colony stimulating factor in patients with advanced pancreatic adenocarcinoma
AUTHOR(S): Kornek, Gabriela; Raderer, Markus; Schenk, Thomas; Pidlich, Johann; Schulz, Franz; Globits, Sebastian; Tetzner, Christine; Scheithauer, Werner

CORPORATE SOURCE: Medical School, Vienna University, Vienna, A-1090, Austria
SOURCE: Cancer (New York) (1995), 76(8), 1356-62
CODEN: CANCAR; ISSN: 0008-543X
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purpose of this study was to determine the maximum tolerated dose (MTD) of a cytotoxic regimen consisting of the second-generation chemosensitizer **dexverapamil** (DVPM), high dose epirubicin, and recombinant human granulocyte-macrophage-colony stimulating factor (GM-CSF) in pancreatic carcinoma. Twenty-eight previously untreated patients with locally advanced or metastatic adenocarcinoma of the pancreas were studied. Treatment consisted of oral DVPM at a dose of 1000-1200 mg/day for 3 days, epirubicin administered as an i.v. bolus injection on Day 2 with an initial dose of 90 mg/m2, and a dose of GM-CSF of 400 μg administered s.c. from Day 5s through 14. Epirubicin dose escalation levels were 90, 105, 120 and 135 mg/m2. Consecutive cohorts of four to eight patients were planned at each dose level. Treatment cycles were repeated every 3 wk. Hematol. toxicity, specifically granulocytopenia, constituted the dose-limiting toxicity with an MTD of 120 mg/m2 for epirubicin. Despite routine supportive therapy with GM-CSF, four, two, and five patients experienced Grade 4 granulocytopenia during their first two treatment courses at levels 105, 120, and 135 mg/m2, resp. Grade 4 granulocytopenia was observed in two, three, and one addnl. patients during subsequent courses with these levels. Nonhematol. toxicity was uncommon, generally modest, and did not correlate clearly with the anthracycline dose. **Dexverapamil**-related cardiovascular symptoms occurred frequently, but they never resulted in serious toxicity requiring active medical intervention or permanent discontinuation of therapy. Nine of 28 patients achieved partial responses to this therapy. Stable disease was observed in nine patients, and **tumor** progress occurred in 10. The MTD of epirubicin for this regimen with DVPM and GM-CSF was 120 mg/m2 every 3 wk. Though it remains uncertain whether the encouraging response activity observed in this disease-oriented Phase I study was, in fact, due to successful modulation of multidrug resistance, these results suggest that this regimen is likely to be an effective and tolerable treatment strategy for patients with pancreatic **cancer**, which should be evaluated further.

L13 ANSWER 40 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:469380 CAPLUS
DOCUMENT NUMBER: 127:185446
TITLE: ATPase activity of P-glycoprotein related to emergence of drug resistance in Ehrlich ascites **tumor** cell lines
AUTHOR(S): Litman, Thomas; Nielsen, Dorte; Skovsgaard, Torben; Zeuthen, Thomas; Stein, Wilfred D.
CORPORATE SOURCE: Department of Oncology, Herlev Hospital, University of Copenhagen, Copenhagen, Den.
SOURCE: Biochimica et Biophysica Acta (1997), 1361(2), 147-158
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The ATPase activities of a sensitive and five progressively daunorubicin-resistant Ehrlich ascites **tumor** cell lines passaged in mice were characterized. For the nine different modulators of drug resistance that the authors have studied, the ATPase activity first rose with the modulator concentration and then declined. The authors analyzed the ATPase activity profiles in terms of an activation constant and an inhibition constant for each of the nine drugs and six cell lines. In this series of cell lines, the drug-stimulatable ATPase activity was directly

proportional to the amount of P-glycoprotein. Pumping of daunorubicin was also correlated with the amount of P-glycoprotein, except that, for a highly passaged line more daunorubicin was pumped than could be accounted for by the content of P-glycoprotein. Between the 12th and the 36th passage an addnl. source of resistance emerged, which was not correlated with P-glycoprotein. Pumping of daunorubicin was neg. correlated with the cell volume for the different lines.

L13 ANSWER 41 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:491023 CAPLUS
DOCUMENT NUMBER: 113:91023
TITLE: Reversal of multi-drug resistance in human KB cell lines by structural analogs of **verapamil**
AUTHOR(S): Pirker, Robert; Keilhauer, Gerhard; Raschack, Manfred; Lechner, Christina; Ludwig, Heinz
CORPORATE SOURCE: 1st Med. Clin., Vienna, A-1090, Austria
SOURCE: International Journal of Cancer (1990), 45(5), 916-19
CODEN: IJCNAW; ISSN: 0020-7136
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several structural analogs of verapamill were studied for their ability to reverse multi-drug resistance (MDR) in human KB cell lines. D595, D792 and verapmill completely reversed resistance to colchicine and adriamycin. D595 and D792 had a higher reversing potency than **verapamil**. Devapamil, gallopamill, emopamil and D528 partially reversed MDR. The reversing potency of a drug did not correlate with its calcium antagonistic activity. No differences in reversing potency between (R)-isomers, (l)-isomers and th racemic forms were observed in the case of both verapamill and emopamil. (R)-Isomers, (L)-isomers and the racemic forms were observed in the case of both **verapamil** and emopamil. (R)-**Verapamil**, which has less calcium antagonistic activity and less in vivo toxicity than racemic **verapamil**, and D792, which has higher reversing potency and less in vivo toxicity than racemic **verapamil**, should be suitable for clin. applications to overcome drug resistance in **cancer** patients.

L13 ANSWER 42 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:692265 CAPLUS
DOCUMENT NUMBER: 121:292265
TITLE: Modulation of adhesion molecule expression on endothelial cells by **verapamil** and other Ca++ channel blockers
AUTHOR(S): Hailer, Nils P.; Blaheta, Roman A.; Harder, Sebastian; Scholz, Martin; Encke, Albrecht; Markus, Bernd H.
CORPORATE SOURCE: Department General Surgery, Hospital the Johann Wolfgang Goethe-University, Frankfurt/Main, Germany
SOURCE: Immunobiology (1994), 191(1), 38-51
CODEN: IMMND4; ISSN: 0171-2985
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cytokine-induced expression of adhesion mols. on leukocytes and endothelial cells (EC) is a crucial point in the process of organ transplant rejection. It has been shown that protein kinase C (PKC) is involved in this activation process. **Verapamil** and other calcium channel blockers seem to possess immunosuppressive qualities in vivo and in vitro; some authors suggested that this is due to PKC- or calmodulin-antagonism. Thus, our objectives were to further investigate the second-messenger systems involved in the stimulation of EC and to analyze whether the beneficial influence of calcium channel blockers on the outcome of transplantation is due to impaired expression of adhesion mols. on EC. Our results, obtained in an in vitro model using human umbilical vein EC, show that IL-1-induced expression of intercellular adhesion mol.-1 (ICAM-1) is in part mediated by PKC and that parallel activation of calmodulin is required. Expression of ICAM-1 was reduced to

38.5% by PKC-inhibitor H7 and to 77.2% by calmodulin-inhibitor W7. In addition, data on the intracellular events in TNF-α-induced expression of vascular cell adhesion mol.-1 (VCAM-1) is presented, showing that both PKC and, to a higher extent, calmodulin, are involved in this process. Expression of VCAM-1 was reduced to 63.7% by H7 and to 27.7% by W7. IL-1-induced expression of endothelial leukocyte adhesion mol.-1 (ELAM-1) is PKC-dependent but insensitive to blocking of calmodulin. Though activation of adhesion mol. expression utilizes PKC and/or calmodulin as second-messenger pathways the investigated calcium channel blockers **verapamil** (R- and S-enantiomers), diltiazem and Ro 40-5967 failed to inhibit adhesion mol. expression.

L13 ANSWER 43 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:644522 CAPLUS
DOCUMENT NUMBER: 131:346221
TITLE: In vitro evaluation of doxorubicin cytotoxicity and cellular uptake in the presence and absence of multidrug resistance modulators
AUTHOR(S): Krishna, Rajesh; Mayer, Lawrence D.
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, V6T 1Z3, Can.
SOURCE: Pharmacy and Pharmacology Communications (1999), 5(8), 511-517
CODEN: PPCOFN; ISSN: 1460-8081
PUBLISHER: Royal Pharmaceutical Society of Great Britain
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cytotoxicity and cellular uptake of doxorubicin was evaluated in the presence and absence of several multidrug resistance (MDR) modulators in the P-glycoprotein overexpressing cell lines, P388/ADR murine lymphocytic leukemia and MCF7/ADR human breast carcinoma. MDR fold-reversal and the residual resistance factor were used to analyze the cytotoxicity results. Newer second generation modulators such as PSC 833, dexniguldipine and Ro11-2933, exhibited higher fold-reversal and lower residual resistance values than first generation modulators, such as **verapamil**. Cytotoxicity data correlated with cellular uptake indicating the blockade of the drug efflux pump. These results emphasize the importance of estimating residual resistance in conjunction with fold-reversal when screening MDR reversing agents for in-vivo application.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 44 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:182574 CAPLUS
DOCUMENT NUMBER: 120:182574
TITLE: Identification of a multidrug resistance modulator with clinical potential by analysis of synergistic activity in vitro, toxicity in vivo and growth delay in a solid human **tumor** xenograft
AUTHOR(S): Plumb, Jane A.; Wishart, G. C.; Setanoians, A.; Morrison, J. G.; Hamilton, T.; Bicknell, S. R.; Kaye, S. B.
CORPORATE SOURCE: CRC Dep. Med. Oncol., Univ. Glasgow, Bearsden/Glasgow, G61 1BD, UK
SOURCE: Biochemical Pharmacology (1994), 47(2), 257-66
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Circumvention of multidrug resistance in vitro by resistance modulators is well documented but their clin. use may be limited by effects on normal tissues. The authors have compared four resistance modifiers, both in terms of modulation of doxorubicin sensitivity in vitro and toxicity in vivo, in order to determine whether it is possible to select agents with clin. potential. **Verapamil**, D-**verapamil** and quinidine are

all maximally active in the multidrug resistant cell line at about 7 μM and are not cytotoxic at this concentration The tiapamil analog Ro11-2933 is a highly potent resistance modulator such that at only 2 μM sensitization is greater than is seen with the other modulators at 7 μM. Since the ID50 concentration for Ro11-2933 is 17.7 μM (5-12-fold less than the other modifiers) the authors have used isobologram anal. to demonstrate that the interaction with doxorubicin is supra-additive and cannot be explained by additive toxicity. This method of anal. also revealed that when resistance modulation is related to the cytotoxicity of the modulator itself, all four modulators show comparable activity. On the other hand, measurement of the acute toxicity in mice of the modulators did reveal differences. The LD10 for **verapamil** (51 mg/kg) was about one third of that for quinidine (185 mg/kg) and this is consistent with the known maximum tolerated plasma levels in patients. Furthermore, while epirubicin alone was unable to reduce the growth rate of a multidrug resistant human **tumor** xenograft, the addition of quinidine, but not **verapamil**, at the maximum tolerated dose did do so. D-**Verapamil** was only about half as toxic as racemic **verapamil** and this too is consistent with clin. observations. The LD10 for Ro11-2933 (152 mg/kg) was comparable with that for quinidine. In the human **tumor** xenograft model maximal growth inhibition was observed with the combination of epirubicin and Ro11-2933 (45 mg/kg) and this degree of growth inhibition was comparable to that obtained with epirubicin alone in the drug sensitive xenografts. Ro11-2933 had no measurable effects on the plasma or **tumor** pharmacokinetics of epirubicin. These results suggest that it is possible to predict the clin. potential of a resistance modulator. Furthermore, Ro11-2933 is a promising agent for use in the clinic since maximal resistance modulation in vivo is observed at about one third of the LD10 dose.

L13 ANSWER 45 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1990:491033 CAPLUS
DOCUMENT NUMBER: 113:91033
TITLE: Effects of calcium antagonists in multidrug resistant primary human renal cell carcinomas
AUTHOR(S): Mickisch, Gerald H.; Koessig, Jutta; Keilhauer, Gerhard; Schlick, Erich; Tschada, Reinhold K.; Alken, Peter M.
CORPORATE SOURCE: Dep. Urol., Mannheim Hosp., Mannheim, D-6800, Germany
SOURCE: Cancer Research (1990), 50(12), 3670-4
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The enhancement of vinblastine cytotoxicity with 4 major classes of Ca-blocking agents was studied in multidrug resistant primary human renal cell carcinomas. Seven different Ca antagonists were selected: **verapamil** (VPM, racemic form), its R-stereoisomer (R-VPM), diltiazem, flunarizine, nifedipine, and its derivs. nimodipine and nitrendipine. **Verapamil** or R-**verapamil** causes a significant decrease of viable **tumor** cells as compared to vinblastine alone. Similar effects were found with diltiazem, nifedipine, and its derivs. reaching .apprx.70% of the VPM/(R)-VPM activity. Flunarizine showed only minor enhancement of cytotoxicity. P-170 glycoprotein expression was demonstrated in 18 of 32 **tumors**, and a relation of chemoresistance was evident. None of the chemoresponders, but 18 or 25 (72%) of the highly resistant **tumors**, revealed this resistance factor. It was concluded that certain Ca antagonists in combination with chemotherapy may well offer therapeutic options in renal cell carcinoma as they apparently inactivate the underlying mechanism conferring resistance. The new stereoisomer, (R)-VPM, in particular, may be used in clin. trials since it combines strong enhancement of vinblastine drug responsiveness with a 10-fold lower cardiovascular activity as compared to racemic VPM, thus allowing higher concns. to be applied.

L13 ANSWER 46 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:20974 CAPLUS
DOCUMENT NUMBER: 140:71069
TITLE: Methods and compositions using hyaluronan receptor ligands for inhibition of multidrug resistance
INVENTOR(S): Toole, Bryan P.
PATENT ASSIGNEE(S): Tufts University, USA
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004003545	A1	20040108	WO 2003-US20918	20030701
WO 2004003545	C2	20040415		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-392905P P 20020701
US 2003-453761P P 20030311

AB Pharmaceutical compns. and methods are provided for sensitizing multidrug-resistant **cancer** or radiation-resistant **cancer** cells to chemotherapeutic agents. Compns. include ligands of hyaluronan receptors, including glycosaminoglycans, e.g. hyaluronan oligomers and derivs. of these oligomers, hyaluronan binding proteins, and antibodies specific for hyaluronan receptors. The multidrug-resistance cells may also be bacterial cells.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 47 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:531074 CAPLUS
DOCUMENT NUMBER: 119:131074
TITLE: Functional expression of P-glycoprotein in apical membranes of human intestinal Caco-2 cells. Kinetics of vinblastine secretion and interaction with modulators
AUTHOR(S): Hunter, Janice; Jepson, Mark A.; Tsuruo, Takashi; Simmons, Nicholas L.; Hirst, Barry H.
CORPORATE SOURCE: Med. Sch., Univ. Newcastle upon Tyne, Newcastle upon Tyne, NE2 4HH, UK
SOURCE: Journal of Biological Chemistry (1993), 268(20), 14991-7
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The functional expression of P-glycoprotein has been studied in confluent epithelial layers of human Caco-2 cells, a polarized, highly differentiated cell line demonstrating an intestinal absorptive cell phenotype. Expression of P-glycoprotein was localized, by indirect immunofluorescence with monoclonal antibody MRK16, to the apical brush-border, approx. 20 μm above the base of the cells. Functional,

high capacity expression of P-glycoprotein in Caco-2 cell layers was demonstrated by the saturable secretion of vinblastine, a typical substrate, from basolateral to apical surfaces: Km 18.99 ± 5.55 μM, Vmax 1285.9 ± 281.2 pmol·cm-2 h-1. The direct correlation of apical P-glycoprotein expression with vinblastine net secretory flux was demonstrated by the reduction of this flux after treatment with MRK16 antibodies. Vinblastine secretory flux was also reduced by treatment with **verapamil** (R- and S-isomers with equal affinity), nifedipine, taxotere, and 1,9-dideoxyforskolin. Kinetic analyses suggest that the inhibition of vinblastine secretory flux by **verapamil** and nifedipine was competitive, while that by dideoxyforskolin was non-competitive, in nature. The polarized expression and activity of P-glycoprotein in Caco-2 cells is direct evidence for its secretory detoxifying function in the **intestine**, subserving at least one role of the gastrointestinal epithelial barrier.

L13 ANSWER 48 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:52021 CAPLUS
DOCUMENT NUMBER: 118:52021
TITLE: Effect of calcium-modifying agents on the growth of human gastric carcinoma cells in vitro
AUTHOR(S): Piontek, Michael; Hengels, Klaus Juergen
CORPORATE SOURCE: Dep. Gastroenterol., Univ. Hosp., Duesseldorf, 4000/1, Germany
SOURCE: Anticancer Research (1992), 12(5), 1559-63
CODEN: ANTRD4; ISSN: 0250-7005
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The antiproliferative effects of various calcium-modifying agents were investigated in human AGS gastric carcinoma cells in culture. Variation of the extracellular calcium concentration, achieved by addition of calcium to the growth medium or binding of calcium to the calcium-chelating agent EDTA, appeared to have little influence on growth of the **tumor** cells. In contrast, the calcium antagonist **verapamil**, the calcium ionophore A 23.187 and the calmodulin antagonist W 7, agents supposed to interfere with the regulation of the intracellular calcium concentration, all exerted marked growth inhibiting effects. These results provide evidence for an important role of intracellular calcium-dependent mechanisms in growth regulation of the human gastric adenocarcinoma cell line AGS.

L13 ANSWER 49 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:996589 CAPLUS
DOCUMENT NUMBER: 124:45676
TITLE: Immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods
INVENTOR(S): Mak, Vivien H. W.
PATENT ASSIGNEE(S): De Novo Corp, USA
SOURCE: PCT Int. Appl., 129 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9527510	A1	19951019	WO 1995-US4677	19950411

W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT,

LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9523857	A1	19951030	AU 1995-23857	19950411	
EP 757558	A1	19970212	EP 1995-917009	19950411	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					
JP 10500669	T2	19980120	JP 1995-526541	19950411	
EP 937460	A2	19990825	EP 1999-201333	19950411	
EP 937460	A3	20000405			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE					
US 5962477	A	19991005	US 1998-97441	19980615	
US 6190691	B1	20010220	US 1998-97440	19980615	

PRIORITY APPLN. INFO.:

US 1994-225991	A2	19940412
US 1994-271287	A	19940706
US 1995-400234	A	19950303
EP 1995-917009	A3	19950411
WO 1995-US4677	W	19950411
US 1995-463819	B1	19950605

AB Screening methods are provided for evaluating compds. capable of suppressing cytokine production either in vitro or in vivo. The methods generally involve stimulating the production of a cytokine in a cell, exposing a portion of the cells to a putative cytokine-modulating agent, and determining subsequent levels of cytokine production in the cells. Addnl., the present invention provides certain compds. identified by this method, as well as methods for treating conditions modulated by TNF. The methodol. of the invention may be used for e.g. prevention or reduction of transdermal drug delivery system-induced irritation and treatment of skin or systemic inflammatory conditions. Examples include e.g. inhibition of stimulated cytokine production in human cells by a variety of drugs. **Verapamil** was effective in preventing the development of skin inflammatory responses in mice.

L13 ANSWER 50 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1992:483058 CAPLUS

DOCUMENT NUMBER: 117:83058

TITLE: Effect of a dihydropyridine analog, 2-[benzyl(phenyl)amino]ethyl 1,4-dihydro-2,6-dimethyl-5-(5,5-dimethyl-2-oxo-1,3,2-dioxaphophorinan-2-yl)-1-(2-morpholinoethyl)-4-(3-nitrophenyl)-3-pyridinecarboxylate on reversing in vivo resistance of **tumor** cells to Adriamycin

AUTHOR(S): Niwa, Kiyoshi; Yamada, Kazutaka; Furukawa, Tatsuhiko; Shudo, Norimasa; Seto, Kiyotomo; Matsumoto, Tamotsu; Takao, Sonshin; Akiyama, Shinichi; Shimazu, Hisaaki

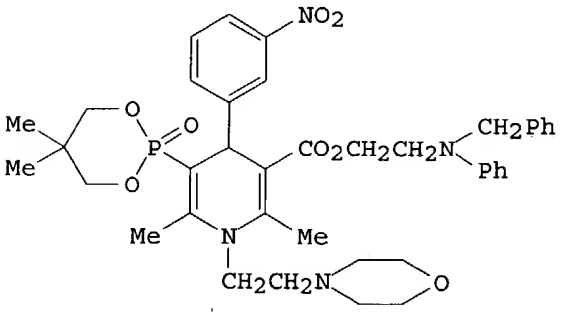
CORPORATE SOURCE: Fac. Med., Kagoshima Univ., Kagoshima, 890, Japan

SOURCE: Cancer Research (1992), 52(13), 3655-60
CODEN: CNREA8; ISSN: 0008-5472

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



I

AB A newly synthesized dihydropyridine analog, PAK-200 (I), at 5 μM inhibited the efflux of [3H]vincristine from KB-C2 cells and increased the accumulation of [3H]vincristine in KB-C2 cells to a level similar to that in KB-3-1 cells. I inhibited the photoaffinity labeling of P-glycoprotein in KB-C2 membranes by [3H]azidopine. At 5 μM, I enhanced the cytotoxic effect of Adriamycin on drug-sensitive KB-3-1 cells, multidrug-resistant KB-8-5 cells, and two human colorectal carcinoma **tumor** lines, COK-28LN and COK-36LN, by factors of 2, 5, 2, and 3 times, resp. The calcium antagonistic activity of I was about 1000 and 5 times lower than that of another dihydropyridine analog, nicardipine, and of **verapamil**, resp. I in combination with Adriamycin completely suppressed the growth of KB-3-1 and COK-36LN and partially suppressed the growth of KB-8-5 but had not significant effect on COK-28LN cells xenografted in nude mice. The level of MDR1 expression of COK-36LN was about 3 times higher than that of COK-28LN, but lower than that of KB-8-5 cells. These results suggest that the interaction of I with P-glycoprotein may be partly correlated with the enhancement of the antitumor effect of Adriamycin on xenografted KB-8-5 and COK-36LN cells in nude mice.

L13 ANSWER 51 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:597931 CAPLUS
DOCUMENT NUMBER: 115:197931
TITLE: Chemotherapy and chemosensitization of transgenic mice which express the human multidrug resistance gene in bone marrow: efficacy, potency, and toxicity
AUTHOR(S): Mickisch, Gerald H.; Licht, Thomas; Merlino, Glenn T.; Gottesman, Michael M.; Pastan, Ira
CORPORATE SOURCE: Lab. Mol. Biol., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SOURCE: Cancer Research (1991), 51(19), 5417-24
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A common form of multidrug resistance in human **cancer** results from expression of MDR1 gene which encodes a plasma membrane energy-dependent multidrug efflux pump. The authors have engineered transgenic mice which express this multidrug transporter in their bone marrow cells and demonstrated that peripheral WBC of these animals provide a rapid and reliable system for assessing the bioactivity of agents that reverse multidrug resistance. Immunocytochem. anal. of bone marrow smears suggests that the activation of the MDR1 transgene has probably occurred at a very early stage of bone marrow differentiation since most bone marrow cells express the transporter. Expression of this transgene in bone marrow produces about 10-fold resistance to leukophenia induced by taxol compared to normal bone marrow. Chemosensitization of MDR1 mice to daunomycin and taxol, measured by a fall in WBC, is detectable at a dose as low as 0.01 mg/kg R-**verapamil**. A dose of 0.5 mg/kg R-**verapamil** reduces the WBC by nearly 50%. Chemosensitization of MDR-transgenic mice with 5 mg/kg R-**verapamil**, which is highly effective in reversing MDR and readily tolerated by mice, necessitates a reduction of the maximum tolerated dose of most chemotherapeutic agents by only 20%. In addition, detailed histopathol. examination shows that treatment of mice with chemotherapeutic drugs and R-**verapamil** does not change the organ-related toxicity pattern but only moderately accentuates inherent toxic side effects of the chemotherapeutic agents. MDR1-Transgenic mice represent a valid model for evaluating efficacy, potency, and toxicity associated with chemotherapy and chemosensitization of multidrug-resistant cells in animals.

L13 ANSWER 52 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:109819 CAPLUS

DOCUMENT NUMBER: 133:37816
TITLE: Liposome encapsulated daunorubicin doubles anthracycline toxicity in cell lines showing a non-PGP related multidrug resistance
AUTHOR(S): Michieli, Mariagrazia; Damiani, Daniela; Ermacora, Anna; Masolini, Paola; Michelutti, Angela; Baccarani, Michele
CORPORATE SOURCE: Division of Hematology, Department of Medical and Morphological Research, Udine University Hospital, Italy
SOURCE: Haematologica (1999), 84(12), 1151-1152
CODEN: HAEMAX; ISSN: 0390-6078
PUBLISHER: Ferrata Storti Foundation
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This work shows that the liposomal formulation of daunorubicin (DaunoXome) doubles daunorubicin toxicity in **tumor** cell lines with an multidrug resistance (MDR)-associated overexpression of multidrug resistance protein (MRP) or lung resistance-associated protein (LRP). The increase in daunorubicin toxicity due to the liposome encapsulation is higher than that produced by adding the MDR modifiers SDZPSC833 or D-**verapamil** to free anthracycline.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 53 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:503600 CAPLUS
DOCUMENT NUMBER: 117:103600
TITLE: Stereoisomers of calcium antagonists which differ markedly in their potencies as calcium blockers are equally effective in modulating drug transport by P-glycoprotein
AUTHOR(S): Hoellt, Volker; Kouba, Monika; Dietel, Manfred; Vogt, Gudrun
CORPORATE SOURCE: Dep. Physiol., Univ. Munich, Munich, D-8000/2, Germany
SOURCE: Biochemical Pharmacology (1992), 43(12), 2601-8
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The (-)-isomer of **verapamil** is 10-fold more potent as a calcium antagonist than the (+)-isomer. However, both enantiomers are equally effective in increasing cellular accumulation of anticancer drugs [Gruber et al., 1988]. In addition to **verapamil**, there exists a wide variety of stereoisomers with phenylalkylamines and dihydropyridine structures which markedly differ in their potency as calcium antagonists. The authors tested these drugs for their ability to increase intracellular accumulation of [3H]vinblastine ([3H]VBL) in a doxorubicin-resistant cell line (F4-6RADR) derived from the Friend mouse leukemia cell line (F4-6P) and in COS-7 monkey kidney cells. Both cell types express substantial amts. of multidrug resistance gene 1 mRNA and P-glycoprotein as revealed by RNA and immuno blot anal. The enantiomers with phenylakylamine structures [(±)-**verapamil**; (±)-devapamil; (±)-emopamil)] and with dihydropyridine structures [(±)-isradipine; (±)-nimodipine; (±)-felodipine; (±)-nitrendipine; (±)-niguldipine] increased [3H]VBL accumulation in both cell lines at micromolar concns. Although the stereoisomers of these drugs differ markedly in their potency as calcium channel blockers, they were about equally effective in increasing VBL levels in the cells. There was no substantial difference in the potencies of the phenylalkylamine drugs in affecting cellular [3H]VBL transport. Major potency differences, however, were observed in the dihydropyridine drug series with the niguldipine isomers as the most effective drugs. Moreover, the niguldipine enantiomers were equally as effective in reversing VBL resistance in F4-6RADR cells as were the the **verapamil** enantiomers. Since (-)-niguldipine (B859-35)

displays a 45-fold lower affinity for calcium channel binding sites than (+)-niguldipine, but is equally potent in inhibiting drug transport by P-glycoprotein and in reversing drug resistance, it may be, in addition to (+)-**verapamil**, another useful candidate drug for the treatment of multidrug resistance in **cancer** patients.

L13 ANSWER 54 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:636053 CAPLUS
DOCUMENT NUMBER: 131:276963
TITLE: Screening methods and therapeutic formulations for cytokine inhibitors
INVENTOR(S): Mak, Vivian
PATENT ASSIGNEE(S): Adolor Corp., USA
SOURCE: U.S., 50 pp., Cont.-in-part of U.S. 400,234, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5962477	A	19991005	US 1998-97441	19980615
WO 9527510	A1	19951019	WO 1995-US4677	19950411
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
EP 937460	A2	19990825	EP 1999-201333	19950411
EP 937460	A3	20000405		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
US 6190691	B1	20010220	US 1998-97440	19980615

PRIORITY APPLN. INFO.:

US 1994-225991	B2	19940412
US 1994-271287	B2	19940706
US 1995-400234	B2	19950303
WO 1995-US4677	A2	19950411
EP 1995-917009	A3	19950411
US 1995-463819	B1	19950605

AB The present invention provides a number of screening methods for evaluating compds. capable of suppressing cytokine production either in vitro or in vivo. The methods generally involve stimulating the production of a cytokine in a cell, exposing a portion of the cells to a putative cytokine modulating agent and determining subsequent levels of cytokine production in the cells. Addnl., the present invention provides certain compds. identified by this method. Therapeutic formulations containing the cytokine inhibitors that are applicable to skin conditions or diseases having an inflammatory and/or immunoallergic component are included in the present invention. Such formulations are useful for relief from chronic and acute conditions, flare-ups and in conjunction with other drug therapies. E.g., a loperamide gel was prepared containing (in percent by weight) loperamide 2.0, Carbopol 940 1.5, and triethanolamine 1.5%, resp., with water making up the reminder.

REFERENCE COUNT: 192 THERE ARE 192 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 55 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:573747 CAPLUS
DOCUMENT NUMBER: 119:173747
TITLE: The effect of ion channel blockers, immunosuppressive

agents, and other drugs on the activity of the multi-drug transporter

AUTHOR(S): Weaver, James L.; Szabo, Gabor, Jr.; Pine, P. Scott; Gottesman, Michael M.; Goldenberg, Sarah; Aszalos, Adorjan

CORPORATE SOURCE: Div. Res. Test., Food Drug Adm., Washington, DC, 20204, USA

SOURCE: International Journal of Cancer (1993), 54(3), 456-61
CODEN: IJCNAW; ISSN: 0020-7136

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The MDR1 protein is an energy-dependent transport protein responsible for the multi-drug resistance seen in many **tumors**. A variety of drugs have been shown to inhibit the function of this pump, including compds. known to block various ion channels. The mouse lymphoma cell line L5178Y has been transduced with the human mdr1 gene. Using this cell line, the authors have tested a number of compds. to determine whether there is a correlation between the ability to block a specific type of ion channel, or shift membrane potential, and the ability to act as an MDR-reversing agent using the fluorescent substrates Rhodamine 123 and daunorubicin as test compds. The authors' results show no apparent correlation between the ability to block a specific ion channel and reversal of MDR transport ability. The authors have found active MDR inhibitors in compds. that affect K+, Na+, Ca2+, H+, but not Cl- channels. The authors' data suggest that Cl- channel activity may be distinct from MDR activity. Several immunosuppressive compds. and analogs were also tested and found to be active reversing agents. Measurements suggest a significant difference in resting membrane potential between the L5178YvMDR line and the L5178Y parental cell line use in these expts. No correlation was found between the ability of drugs to alter membrane potential and to inhibit MDR transport activity. The authors' results suggest that MDR transport function may be independent of the physiol. movement of ions and show that a wide variety of compds. can inhibit MDR transport.

L13 ANSWER 56 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1991:94766 CAPLUS

DOCUMENT NUMBER: 114:94766

TITLE: Transgenic mice that express the human multidrug-resistance gene in bone marrow enable a rapid identification of agents that reverse drug resistance

AUTHOR(S): Mickisch, Gerald H.; Merlino, Glenn T.; Galski, Hanan; Gottesman, Michael M.; Pastan, Ira

CORPORATE SOURCE: Lab. Mol. Biol., Natl. Cancer Inst., Bethesda, MD, 20892, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1991), 88(2), 547-51
CODEN: PNASA6; ISSN: 0027-8424

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The development of preclin. models for the rapid testing of agents that circumvent multidrug resistance in **cancer** is a high priority of research on drug resistance. A common form of multidrug resistance in human **cancer** results from expression of the MDR1 gene, which encodes a Mr 170,000 glycoprotein that functions as a plasma membrane energy-dependent multidrug efflux pump. Transgenic mice that express this multidrug transporter in their bone marrow were engineered; these animals are resistant to leukopenia by a panel of anticancer drugs including anthracyclines, vinca alkaloids, etoposide, taxol, and actinomycin D. Differential leukocyte counts indicate that both neutrophils and lymphocytes are protected. Drugs such as cisplatin, methotrexate, and 5-fluorouracil, which are not handled by the multidrug transporter, produce bone marrow suppression in both normal and transgenic mice. The

L6 ANSWER 5 OF 30 MEDLINE on STN
ACCESSION NUMBER: 93111928 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1281979
TITLE: Formyl peptides and ATP stimulate Ca2+ and Na+ inward currents through non-selective cation channels via G-proteins in dibutyryl cyclic AMP-differentiated HL-60 cells. Involvement of Ca2+ and Na+ in the activation of beta-**glucuronidase** release and superoxide production.
AUTHOR: Krautwurst D; Seifert R; Hescheler J; Schultz G
CORPORATE SOURCE: Institut fur Pharmakologie, Freie Universitat Berlin, Federal Republic of Germany.
SOURCE: Biochemical journal, (1992 Dec 15) 288 (Pt 3) 1025-35. Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199301
ENTRY DATE: Entered STN: 19930212
Last Updated on STN: 20000303
Entered Medline: 19930128

AB In human neutrophils, the chemotactic peptide N-formyl-L-methionyl-L-leucyl-L-phenylalanine (fMLP) induces increases in the intracellular free Ca2+ concentration ([Ca2+]i) with subsequent activation of beta-**glucuronidase** release and superoxide (O2-) production. Results from several laboratories suggest that the increase in [Ca2+]i is due to activation of non-selective cation (NSC) channels. We studied the biophysical characteristics, pharmacological modulation and functional role of NSC channels in dibutyryl cyclic AMP (Bt2cAMP)-differentiated HL-60 cells. fMLP increased [Ca2+]i by release of Ca2+ from intracellular stores and influx of Ca2+ from the extracellular space. fMLP also induced Mn2+ influx. Ca2+ and Mn2+ influxes were inhibited by 1-(beta-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl)-1H-imidazole hydrochloride (SK&F 96365). Under whole-cell voltage-clamp conditions, fMLP and ATP (a purinoceptor agonist) activated inward currents characterized by a linear current-voltage relationship and a reversal potential near 0 mV. NSC channels were substantially more permeable to Na+ than to Ca2+. SK&F 96365 inhibited fMLP- and ATP-stimulated currents with a half-maximal effect at about 3 microM. Pertussis toxin prevented stimulation by fMLP of NSC currents and reduced ATP-stimulated currents by about 80%. Intracellular application of the stable GDP analogue, guanosine 5'-O-[2-thio]diphosphate, completely blocked stimulation by agonists of NSC currents. In excised inside-out patches, single channel openings with an amplitude of 0.24 pA were observed in the presence of fMLP and the GTP analogue, guanosine 5'-O-[3-thio]triphosphate. The bath solution contained neither Ca2+ nor ATP. The current/voltage relationship was linear with a conductance of 4-5 pS and reversed at about 0 mV. fMLP-induced beta-**glucuronidase** release and O2- production were substantially reduced by replacement of extracellular CaCl2 or NaCl by ethylenebis(oxyethylenenitrilo)tetra-acetic acid and choline chloride respectively. In the absence of Ca2+ and Na+, fMLP was ineffective. SK&F 96365 inhibited fMLP-induced beta-**glucuronidase** release and O2- production in the presence of both Ca2+ and Na+, and in the presence of Ca2+ or Na+ alone. NaCl (25-50 mM) enhanced the basal and absolute extent of fMLP-stimulated GTP hydrolysis of heterotrimeric regulatory G-proteins in HL-60 membranes. The order of effectiveness of salts in enhancing GTP hydrolysis was LiCl > KCl > NaCl > choline chloride.(ABSTRACT TRUNCATED AT 400 WORDS)

L6 ANSWER 2 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:977175 CAPLUS
DOCUMENT NUMBER: 140:280930
TITLE: Verapamil regulates activity and mRNA-expression of human β- **glucuronidase** in HepG2 cells
AUTHOR(S): Grube, M.; Kunert-Keil, C.; Sperker, B.; Kroemer, H. K.
CORPORATE SOURCE: Department of Pharmacology, Peter Holtz Research Center of Pharmacology and Experimental Therapeutics, Friedrich Loefflerstrasse 23d, Greifswald, 17487, Germany
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (2003), 368(6), 463-469
CODEN: NSAPCC; ISSN: 0028-1298
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A promising development in tumor therapy is the application of non-toxic prodrugs from which the active cytostatic is released by endogenous enzymes such as β- **glucuronidase** (β-gluc). Regulation of β-gluc expression is one crucial factor modulating bioactivation of prodrugs. Recent expts. in rats indicate regulation of β-gluc activity by the **calcium channel** blocker verapamil. To further explore this phenomenon, we investigated the effect of verapamil on β-gluc enzyme activity, protein (western blot) and mRNA expression (RT-PCR) as well as the underlying mechanisms (effects of verapamil metabolites; promoter activity) in the human hepatoma cell line HepG2. Treatment of HepG2 cells with verapamil revealed down-regulation of β-gluc activity, protein, and mRNA level down to 50% of the control with EC50 values of 25 μM. Effects were similar for both enantiomers. Moreover, it was demonstrated that reduced promoter activity contributes to the observed effects. In summary, our data demonstrate regulation of human β- **glucuronidase** expression by verapamil. Based on our findings we hypothesize that coadministration of verapamil may effect cleavage of glucuronides by β- **glucuronidase**.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2003592287 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14618298
TITLE: Verapamil regulates activity and mRNA-expression of human beta-**glucuronidase** in HepG2 cells.
AUTHOR: Grube M; Kunert-Keil C; Sperker B; Kroemer H K
CORPORATE SOURCE: Department of Pharmacology, Peter Holtz Research Center of Pharmacology and Experimental Therapeutics, Friedrich Loefflerstrasse 23d, 17487 Greifswald, Germany.
SOURCE: Naunyn-Schmiedeberg's archives of pharmacology, (2003 Dec) 368 (6) 463-9.
Journal code: 0326264. ISSN: 0028-1298.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 20031216
Last Updated on STN: 20040618
Entered Medline: 20040617

AB A promising development in tumor therapy is the application of non-toxic prodrugs from which the active cytostatic is released by endogenous enzymes such as beta-**glucuronidase** (beta-gluc). Regulation of beta-gluc expression is one crucial factor modulating bioactivation of prodrugs. Recent experiments in rats indicate regulation of beta-gluc activity by the **calcium channel** blocker verapamil.To further explore this phenomenon, we investigated the effect of verapamil on beta-gluc enzyme activity, protein (western blot) and mRNA expression (RT-PCR) as well as the underlying mechanisms (effects of verapamil metabolites; promoter activity) in the human hepatoma cell line HepG2.Treatment of HepG2 cells with verapamil revealed down-regulation of beta-gluc activity, protein, and mRNA level down to 50% of the control with EC(50) values of 25 microM. Effects were similar for both enantiomers. Moreover, it was demonstrated that reduced promoter activity contributes to the observed effects. In summary, our data demonstrate regulation of human beta-**glucuronidase** expression by verapamil. Based on our findings we hypothesize that coadministration of verapamil may effect cleavage of glucuronides by beta-**glucuronidase**.

resistance conferred by the MDR1 gene can be circumvented in a dose-dependent manner by simultaneous administration of agents previously shown to be inhibitors of the multidrug transporter in vitro, including **verapamil** isomers, quinidine, and quinine. **Verapamil** and quinine, both at levels suitable for human trials that produced only partial sensitization of the MDR1-transgenic mice, were fully sensitizing when used in combination. Thus, MDR-1 transgenic mice provide a rapid and reliable system to determine the bioactivity of agents that reverse multidrug resistance in animals.

L13 ANSWER 57 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:483372 CAPLUS
DOCUMENT NUMBER: 125:131535
TITLE: Inhibitors of P-Glycoprotein-Mediated Daunomycin Transport in Rat Liver Canalicular Membrane Vesicles
AUTHOR(S): Kwon, Younggil; Kamath, Amrita V.; Morris, and Marilyn E.
CORPORATE SOURCE: School of Pharmacy, State University of New York, Amherst, NY, 14260, USA
SOURCE: Journal of Pharmaceutical Sciences (1996), 85(9), 935-939
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB P-glycoprotein (P-gp), the multidrug resistance (MDR) gene product, is exclusively located on the canalicular membrane of hepatocytes. Recent studies using isolated rat canalicular liver plasma membrane (cLPM) vesicles indicate that daunomycin (DNM) is a substrate for the ATP-dependent P-gp efflux system in the rat liver. The isoforms of P-gp present in cLPM and in **cancer** cell lines differ in that the major form present in the liver represents the gene product of mdr2 in mice (MDR3 in humans; class III) while the isoform of P-gp in **cancer** cells is the gene product of mdr1 in mice (MDR1 in humans, class I). The objective of this study was to examine the inhibitory effects of various organic compds., most of which have been studied previously in MDR **cancer** cells, on P-gp-mediated [3H]DNM uptake into cLPM. Also, the stereospecificity of P-gp for its substrates was investigated by comparing the inhibitory effects of the enantiomers and the racemic mixts. of **verapamil** and propranolol. DNM exhibited ATP-dependent active transport into rat liver cLPM with a Km of 26.8 ± 13.4 μM and a Vmax of 4.9 ± 0.8 nmol/45 s/mg of protein (n = 4). ADP, AMP, and a nonhydrolyzable ATP analog did not increase DNM transport over the control value. Thirty-one potential inhibitors were examined; only acridine orange, doxorubicin, **verapamil**, propranolol, phosphatidylcholine, β-estradiol glucuronide, and DNM itself showed statistically significant inhibition of [3H]DNM uptake into cLPM. These results suggest that only a limited number of substrates bind to or are transported across the hepatic canalicular membrane via P-gp. Phosphatidylcholine, a substrate for the gene product of the class III P-gp gene, produced significant inhibition of [3H]DNM transport (30.6% at a 10-fold-higher substrate concentration), suggesting that transport may be mediated, at least in part, by this P-gp gene product. There were no statistically significant differences in the inhibitory effects of the enantiomers and racemate of **verapamil** on [3H]DNM transport into cLPM, but the enantiomers of propranolol exhibited stereospecific inhibition of DNM transport. (R)-(+)-Propranolol produced a statistically significant inhibition of [3H]DNM transport similar to that observed with the racemic mixture, while (S)(-)-propranolol showed no inhibition. These findings suggest that bile canalicular P-gp may exhibit stereospecificity of binding or transport for its substrates.

L13 ANSWER 58 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:602315 CAPLUS

DOCUMENT NUMBER: 130:10356
TITLE: Vinflunine (20',20'-difluoro-3',4'-dihydrovinorelbine), a novel Vinca alkaloid, which participates in P-glycoprotein (Pgp)-mediated multidrug resistance in vivo and in vitro
AUTHOR(S): Etievant, Chantal; Barret, Jean-Marc; Kruczynski, Anna; Perrin, Dominique; Hill, Bridget T.
CORPORATE SOURCE: Division de Cancerologie Experimentale I, Centre de Recherche Pierre Fabre, Castres, Fr.
SOURCE: Investigational New Drugs (1998), 16(1), 3-17
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Vinflunine (VFL) is a novel derivative of vinorelbine (NVB, Navelbine®) which has shown markedly superior antitumor activity to NVB, in various exptl. animal models. To establish whether this new Vinca alkaloid participates in P-glycoprotein (Pgp)-mediated multidrug resistance (MDR), VFL-resistant murine P388 cells (P388/VFL) were established in vivo and used in conjunction with the well established MDR P388/ADR subline, to define the in vivo resistance profile for VFL. P388/VFL cells proved cross-resistant to drugs implicated in MDR (other Vinca alkaloids, doxorubicin, etoposide), but not to campothecin or cisplatin and showed an increased expression of Pgp, without any detectable alterations in topoisomerase II or in glutathione metabolism The P388/ADR cells proved cross-resistant to VFL both in vivo and in vitro, and this VFL resistance was efficiently modulated by **verapamil** in vitro. Cellular transport expts. with tritiated-VFL revealed differential uptake by P388 sensitive and P388/ADR resistant cells, comparable with data obtained using tritiated-NVB. In various in vitro models of human MDR **tumor** cells, while full sensitivity was retained in cells expressing alternative non-Pgp-mediated MDR mechanisms, cross resistance was identified in Pgp-overexpressing cells. Differences were, however, noted in terms of the drug resistance profiles relative to the other Vincas, with **tumor** cell lines proving generally least cross-resistant to VFL. Overall, these results suggest that VFL, like other Vinca alkaloids, participates in Pgp-mediated MDR, with **tumor** cells selected for resistance to VFL overexpressing Pgp, yet MDR **tumor** cell lines proved generally less cross resistant to VFL relative to the other Vinca alkaloids.
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 59 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:654031 CAPLUS
DOCUMENT NUMBER: 125:316421
TITLE: Effects of the selective bisindolylmaleimide protein kinase C inhibitor GF 109203X on P-glycoprotein-mediated multidrug resistance
AUTHOR(S): Gekeler, V.; Boer, R.; Ueberall, F.; Ise, W.; Schubert, C.; Utz, I.; Hofmann, J.; Sanders, K. H.; Schaechtele, C.; et al.
CORPORATE SOURCE: Byk Gulden GmbH, Konstanz, D-78403, Germany
SOURCE: British Journal of Cancer (1996), 74(6), 897-905
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Inhibition of protein kinase C (PKC) is discussed as a new approach for overcoming multidrug resistance (MDR) in **cancer** chemotherapy. For evaluation of this concept we applied the bisindolymaleimide GF 109203X, which shows a highly selective inhibition of PKC isoenzymes α, β1, β2, γ, δ and ε in vitro. The efficacy of this compound in modulation of MDR was examined using several

P-glycoprotein (P-gp)-overexpressing cell lines including a MDR1-transfected HeLa clone, and was compared with the activities of dexniguldipine-HCl (DNIG) and **dexverapamil**-HCl (DVER), both of which essentially act via binding to P-gp. As PKCα has been suggested to play a major role in P-gp-mediated MDR, cell lines exhibiting different expression levels of this PKC isoenzyme were chosen. On crude PKC prepns. or in a cellular assay using a cfos(-711)CAT-transfected NIH 3T3 clone, the inhibitory qualities of the bisindolylmaleimide at submicromolar concns. were demonstrated. At up to 1 μM final concns. of the PKC inhibitor GF 109203X, a concentration at which many PKC isoenzymes should be blocked substantially, no cytotoxic or MDR-reversing effects whatsoever were seen, as monitored by 72 h tetrazolium-based colorimetric MTT assays or a 90 min rhodamine 123 accumulation assay. Moreover, depletion of PKCα by phorbol ester in HeLa-MDR1 transfectants had no influence on rhodamine 123 accumulation after 24 or 48 h. MDR reversal activity of GF 109203X was seen at higher final drug concns., however. Remarkably, [3H]vinblastine-sulfate binding competition expts. using P-gp-containing crude membrane prepns. demonstrated similar dose dependencies as found for MDR reversion by the three modulators, i.e. decreasing efficacy in the series dexniguldipine-HCl>**dexverapamil**-HCl>GF 109203X. Similar interaction with the P-gp in the micromolar concentration range was revealed by competition of GF 109203X with photoincorporation of [3H]azidopine into P-gp-containing crude membrane prepns. No significant effect of the PKC inhibitor on MDR1 expression was seen, which was examined by cDNA-PCR. Thus, the bisindolylmaleimide GF 109203X probably influences MDR mostly via direct binding to P-gp. Our work identifies the bisindolylmaleimide GF 109203X as a new type of drug interacting with P-gp directly, but does not support the concept of a major contribution of PKC to a P-gp-associated MDR, at least using the particular cellular model systems and the selective, albeit general, PKC inhibitor GF 109203X.

L13 ANSWER 60 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:182916 CAPLUS
DOCUMENT NUMBER: 124:277796
TITLE: Sensitive and rapid bioassay for analysis of P-glycoprotein-inhibiting activity of chemosensitizers in patient serum
AUTHOR(S): Lehnert, Manfred; de Giuli, Rita; Twentyman, Peter R.
CORPORATE SOURCE: Cancer Res. Lab., Dep. C Internal Medicine, Gallen, CH-9007, Switz.
SOURCE: Clinical Cancer Research (1996), 2(2), 403-10
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Clin. studies of agents capable of reversing P-glycoprotein (Pgp)-mediated multidrug resistance have attracted much attention in recent years. One question of interest in such studies is whether the concns. achieved by chemosensitizers are sufficient to inhibit Pgp function. The goal of the present study was to develop a reliable ex vivo bioassay for anal. of the Pgp-inhibiting activity of chemosensitizer-containing patient serum. The fluorescent Pgp substrates daunorubicin (DNR) and rhodamine 123 (R123) were used as probes for Pgp function. The 8226/DOX6 human myeloma cell line, which expresses Pgp at levels that can be detected in clin. **cancers**, was used as a model system. The index chemosensitizers tested were **dexverapamil** (DVPM) and cyclosporin A, with particular focus on DVPM. Using flow cytometry, chemosensitizer effects on 1-h drug accumulation and on drug retention at 30 min were evaluated. In the studies using pooled human serum spiked in vitro with graded chemosensitizer concns., the order of assay sensitivity was R123 retention >>> R123 accumulation > DNR retention equal to DNR accumulation. Keeping serum spiked with DVPM for several hours at room temperature or 4°C or for several months at -80°C had no effect on Pgp-blocking activity.

Sixteen blood samples from patients with metastatic breast **cancer** receiving DVPM to overcome epirubicin resistance were analyzed for Pgp-inhibiting activity and for levels of DVPM and nor-DVPM, the major metabolite of **verapamil**. Each patient sample was found capable of increasing R123 retention in the 8226/DOX6 cells, with activity factors of 3- to 8-fold and good agreement between DVPM blood levels and bioassay activity ($r = 0.7168$; two-sided $P = 0.0018$). The R123 retention assay developed and validated in this study seems to be a sensitive, reproducible, and easy-to-use method for anal. of Pgp-inhibiting activity of chemosensitizer-containing human serum. The assay seems capable of estimating DVPM blood levels and could prove to be a valuable tool for monitoring chemosensitizer treatment in **cancer** patients.

L13 ANSWER 61 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:226154 CAPLUS
DOCUMENT NUMBER: 128:292440
TITLE: A novel bioassay for P-glycoprotein functionality using cytochalasin D
AUTHOR(S): Elbling, Leonilla; Berger, Walter; Weiss, Rosa-Maria; Printz, Dieter; Fritsch, Gerhard; Micksche, Michael
CORPORATE SOURCE: Institute of Tumor Biology-Cancer Research, Department of Applied and Experimental Oncology, Vienna University, Vienna, A-1090, Austria
SOURCE: Cytometry (1998), 31(3), 187-198
CODEN: CYTODQ; ISSN: 0196-4763
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The functional contribution of both P-glycoprotein (P-gp) and the multidrug resistance-associated protein (MRP) to multidrug resistance (MDR) in **tumor** cells is commonly determined by drug cytotoxicity and/or accumulation/efflux tests. The authors report on a bioassay developed for the specific detection of functional P-gp levels and the efficacy of related chemosensitizers (CD-P-gp-assay). The assay is based on the flow cytometric measurement of changes in the ≥G2M cell cycle compartment which are due to the induction of polykaryons after exposure of proliferating cells to three defined cytochalasin D (CD) concns. with and without **verapamil**. As demonstrated in 13 well-characterized MDR cell models (20 resistant sublines), there is a significant correlation between cytokinesis-blocking CD doses, as well as responsiveness to chemosensitizers and MDR1 gene expression (mRNA and P-gp) allowing discrimination between different levels of P-gp-MDR. CD-P-gp-assay specificity was assessed by testing 23 compds.: 19 known as potent inhibitors of P-gp-MDR, some of them, though to a lesser extent, also of MRP-MDR; 1 inhibiting MRP-but not P-gp-MDR; 3 inactive in both types of MDR. A modulation of CD activity was confined exclusively to both P-gp-expressing cell lines and P-gp chemosensitizers. CD cytoskeletal activity measured by FACS is a specific and sensitive tool with which to detect functional P-gp and related chemosensitizers.
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 62 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:400225 CAPLUS
DOCUMENT NUMBER: 115:225
TITLE: Modulation of mitomycin C-induced multidrug resistance in vitro
AUTHOR(S): Dorr, Robert T.; Liddil, James D.
CORPORATE SOURCE: Coll. Med., Univ. Arizona, Tucson, AZ, 85724, USA
SOURCE: Cancer Chemotherapy and Pharmacology (1991), 27(4), 290-4
CODEN: CCPHDZ; ISSN: 0344-5704
DOCUMENT TYPE: Journal

LANGUAGE: English

AB A series of in vitro cytotoxicity studies were performed to achieve pharmacol. reversal of resistance to the alkylating agent mitomycin (MMC) in L-1210 leukemia cells. A multidrug-resistant (MDR), P-glycoprotein-pos. cell line, RL-1210/.1, was exposed to potential MDR modulators in the absence or presence of MMC. The following compds. did not reverse MMC-induced MDR: quinine, quinidine, lidocaine, procaine, dimethylsulfoxide (DMSO), dexamethasone, hydrocortisone, prednisolone, estradiol, and testosterone. Three agents were capable of reversing MMC resistance: progesterone, cyclosporin A, and **verapamil**. The R- and S-isomers of **verapamil** were equipotent, although they showed a 10-fold difference in cardiovascular potency (S > R). Some agents produced cytotoxic effects in MDR cells in the absence of MMC, including progesterone, quinine, and quinidine. The results suggest that R-**verapamil** and progesterone may have clin. utility in reversing MMC resistance in human **tumors**. Progesterone may be uniquely efficacious due to its low toxicity in normal cells, its selective cytotoxicity in MDR cells (in the absence of MMC), and its ability to reverse MMC resistance in vitro. The findings also suggest that the P-glycoprotein induced by MMC differs from that induced by doxorubicin, which is highly sensitive to modulation by lysosomotropic amines such as quinine and quinidine.

L13 ANSWER 63 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:791549 CAPLUS

DOCUMENT NUMBER: 130:148249

TITLE: Human liver microsomal metabolism of paclitaxel and drug interactions

AUTHOR(S): Desai, Pankaj B.; Duan, John Z.; Zhu, Y.-W.; Kouzi, S.

CORPORATE SOURCE: Division Pharmaceutical Sciences, College Pharmacy, Medical Center, University Cincinnati, Cincinnati, OH, 45267, USA

SOURCE: European Journal of Drug Metabolism and Pharmacokinetics (1998), 23(3), 417-424
CODEN: EJDPD2; ISSN: 0378-7966

PUBLISHER: Medecine et Hygiene

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The influence was investigated of anticancer drugs and investigational multidrug resistance (MDR) reversing agents on the hepatic metabolism of paclitaxel (Taxol) to its primary metabolites, 6α-hydroxypaclitaxel (MA) and 3'-p-hydroxypaclitaxel (MB). There is an inter-individual variability associated with the levels of these 2 metabolites. In many cases, 6α-hydroxypaclitaxel was the predominant metabolite, in others, 3'-p-hydroxypacli-taxel was principal metabolite. The formation of 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel is catalyzed by cytochrome P 450 isoenzymes CYP2CS and CYP3A4, resp. A number of factors, including co-administration of drugs and adjuvants, influence the activity of these isoenzymes. The influence of MDR reversing agents, R-**verapamil**, cyclosporin A (CsA), and tamoxifen and anti-**cancer** drugs doxorubicin, etoposide (VP-16), and cisplatin on paclitaxel metabolism was assessed employing human liver microsomes in vitro. Paclitaxel (10 μM) was incubated with human liver microsomes (1 mg protein, -0.34 nmol) in the presence of a NADPH generating system at 37° for 1 h, with and without the presence of interacting drug. Controls included incubations with quercetin and ketoconazole, known inhibitors of 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel formation, resp. At the end of the incubation period, paclitaxel and the metabolites were extracted in Et acetate and analyzed by HPLC. Inhibition of paclitaxel conversion to 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel was observed in the presence of R-**verapamil**, tamoxifen, and VP-16. Doxorubicin inhibited the formation of 3'-p-hydroxypaclitaxel and CsA inhibited the formation of 6α-hydroxypaclitaxel. This study demonstrates that

co-administration of several of the above listed compds. could lead to significant changes in the pharmacokinetics of paclitaxel.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 64 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:783950 CAPLUS

DOCUMENT NUMBER: 132:9021

TITLE: Methods and agents for modulating the immune response and inflammation involving monocyte and dendritic cell membrane proteins

INVENTOR(S): Beaulieu, Sylvie; Randolph, Gwendalyn J.; Muller, William A.; Steinman, Ralph M.

PATENT ASSIGNEE(S): The Rockefeller University, USA; The Cornell Research Foundation

SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9962537	A1	19991209	WO 1999-US12681	19990604
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9944237	A1	19991220	AU 1999-44237	19990604

PRIORITY APPLN. INFO.: US 1998-90781 19980604
WO 1999-US12681 19990604

AB Methods and agents are provided to decrease or increase the migration of dendritic cells for the suppression or enhancement, resp., of the development of immunity and the immune response, by modulating the dendritic cell membrane proteins p-glycoprotein (MDR-1) and tissue factor. Agents which suppress migration have utility in the treatment of immunol.-mediated and inflammatory diseases, e.g. graft rejection, contact dermatitis, seasonal allergies, asthma, and food allergies. Agents which enhance migration are useful for increasing the effectiveness of vaccines. Agents are also disclosed which enhance the migration of monocytes, useful in the treatment of chronic inflammatory diseases. Methods are also provided for identifying useful agents by measuring the effect on dendritic cell migration of agents which modulate p-glycoprotein and tissue factor activity, as well as the effect of agents on monocyte migration.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 65 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:306881 CAPLUS

DOCUMENT NUMBER: 140:367968

TITLE: P glycoprotein in human immunodeficiency virus type 1 infection and therapy

AUTHOR(S): Sankatsing, Sanjay U. C.; Beijnen, Jos H.; Schinkel, Alfred H.; Lange, Joep M. A.; Prins, Jan M.

CORPORATE SOURCE: Department of Internal Medicine, Division of Infectious Diseases, Tropical Medicine and AIDS, Academic Medical Center, International Antiviral Therapy Evaluation Center, University of Amsterdam, Amsterdam, Neth.

SOURCE: Antimicrobial Agents and Chemotherapy (2004), 48(4), 1073-1081
CODEN: AMACCQ; ISSN: 0066-4804

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. With the advent and widespread use of potent antiretroviral therapy in the mid-1990s, the clin. course of human immunodeficiency virus (HIV) type 1-(HIV-1) infection has changed dramatically in a substantial proportion of HIV-1-infected in -dividuals. This has led to a significant decline in the incidence of AIDS and AIDS-related morbidity and mortality in the developed world. Protease inhibitors in combination with inhibitors of HIV-1 reverse transcriptase cause a dramatic reduction in plasma viremia, with the plasma HIV-1 RNA load being below the limit of detection in many patients. However, with the currently available drugs, complete eradication of HIV-1 from an infected person is not achieved because of the persistence of latently infected, resting CD4+ T cells harboring replication-competent HIV-1 and because of ongoing low-level viral replication. One cause of ongoing viral replication can be suboptimal penetration of drugs into anatomical sanctuary sites like the central nervous system. It has been suggested that drug transporters like P glycoprotein (P-gp) may contribute to this suboptimal penetration. Such drug transporters might also lower intracellular drug levels, thereby limiting the therapeutic effi-cacies of antiviral drugs in peripheral blood mononuclear cells (PBMCs), including CD4+ T cells. P-gp, a plasma membrane protein encoded by the multidrug resistance (MDR) gene, was discovered in 1976 (71) and functions as an AT P-dependent drug efflux pump. It is a transporter of a wide range of compds., including hydrophobic amphipathic drugs, calcium channel blockers, antihistamines, peptides, and steroids. The function of P-gp is thoroughly investigated in the oncol. field because of its ability to induce resistance to anticancer therapy by pumping the drugs out of **tumor** cells. In this minireview we summarize the possible roles of P-gp in HIV-1 infection and therapy.

REFERENCE COUNT: 154 THERE ARE 154 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 66 OF 66 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:400101 CAPLUS
DOCUMENT NUMBER: 127:23742
TITLE: Method, compositions and kits for increasing the oral bioavailability of pharmaceutical agents
INVENTOR(S): Broder, Samuel; Duchin, Kenneth L.; Selim, Sami
PATENT ASSIGNEE(S): Baker Norton Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 136 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9715269	A2	19970501	WO 1996-IB1485	19961024
WO 9715269	A3	19970731		
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5968972	A	19991019	US 1996-608776	19960229
US 6245805	B1	20010612	US 1996-733142	19961016
AU 9712056	A1	19970515	AU 1997-12056	19961024
AU 698142	B2	19981022		
EP 794794	A1	19970917	EP 1996-943268	19961024

R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE

JP 10509741	T2	19980922	JP 1996-516449		19961024
BR 9607066	A	20021210	BR 1996-7066		19961024
JP 3361102	B2	20030107	JP 1997-516449		19961024
RU 2217135	C2	20031127	RU 1997-112888		19961024
ZA 9609001	A	19970617	ZA 1996-9001		19961025
NO 9702968	A	19970723	NO 1997-2968		19970625
PRIORITY APPLN. INFO.:			US 1995-7071P	P	19951026
			US 1996-608776	A	19960229
			US 1996-733142	A	19961016
			WO 1996-IB1485	W	19961024

AB A method of increasing the bioavailability upon oral administration of a pharmacol. active target agent, particularly an antitumor or antineoplastic agent which exhibits poor or inconsistent oral bioavailability (e.g., paclitaxel, docetaxel or etoposide), comprises the oral co-administration to a mammalian patient of the target agent and an oral bioavailability-enhancing agent (e.g., cyclosporin A, cyclosporin D, cyclosporin F, or ketoconazole). The oral bioavailability-enhancing agents are known to be MDR (P-glycoprotein) inhibitors. The enhancing agent may be administered orally from 0.5-24 h prior to the oral administration of one or more doses of the target agent, substantially simultaneously with the target agent, or both prior to and substantially simultaneously with the target agent. A method of treating mammalian patients suffering from diseases responsive to target agents with poor oral bioavailability, as well as oral dosage forms containing such target agents, combination oral dosage forms containing bioavailability-enhancing agents and target agents kits containing enhancing and target agent dosage forms and dosing information for the co-administration of the same are also disclosed.

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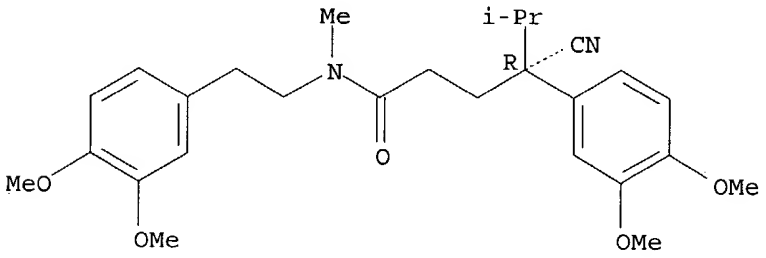
L11 ANSWER 5 OF 67 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:548839 CAPLUS
DOCUMENT NUMBER: 127:214774
TITLE: Treatment of advanced colorectal **cancer** with doxorubicin combined with two potential multidrug-resistance-reversing agents. High-dose oral tamoxifen and dexverapamil
AUTHOR(S): Weinlander, G.; Kornek, G.; Raderer, M.; Hejna, M.; Tetzner, C.; Scheithauer, W.
CORPORATE SOURCE: Medical School, University Vienna, Vienna, A-1090, Austria
SOURCE: Journal of Cancer Research and Clinical Oncology (1997), 123(8), 452-455
CODEN: JCROD7; ISSN: 0171-5216
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB On the basis of the overexpression of the MDR1 gene in human colorectal **cancer**, which may constitute a mol. basis for intrinsic drug resistance that can be reversed, and because of the limited therapeutic value of conventional cytotoxic treatment in this disease, the present phase II study of P-glycoprotein-directed double modulation was initiated. Fifteen patients with measurable metastatic colorectal **cancer**, all of whom were refractory to 1st-line chemotherapy with 5-fluorouracil/leukovorin, were entered in this trial. Treatment consisted of 80 mg tamoxifen twice daily on days 1-9, oral dexverapamil every day on days 7-9, and 60 mg/m2 doxorubicin given by i.v. bolus injection on day 8. Courses were repeated every 4 wk. After a median of 3 courses, none of the 14 evaluable patients had objective response, and 4 had stable disease. Adverse reactions consisted mainly of myelosuppression (WHO grade IV granulocytopenia was noted in 40%), and mild and reversible dexverapamil-related cardiovascular side-effects, specifically hypotension (47%). Thus, despite the histol. demonstration of high levels of P-glycoprotein in colorectal **cancer** and administration of 2 potentially synergistic chemosensitizers, the authors were unsuccessful in circumventing its primary resistance to chemotherapy.

L1 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 302825-79-2 REGISTRY
CN Benzenebutanamide, γ-cyano-N-[2-(3,4-dimethoxyphenyl)ethyl]-3,4-dimethoxy-N-methyl-γ-(1-methylethyl)-, (γR)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **(R)-Verapamilamide**
FS STEREOSEARCH
MF C27 H36 N2 O5
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: PREP (Preparation); RACT (Reactant or reagent)

Absolute stereochemistry.



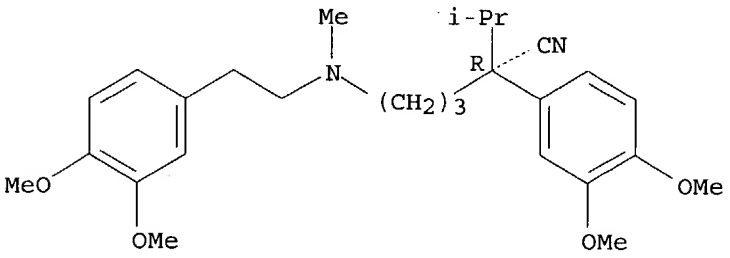
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 38321-02-7 REGISTRY
CN Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-α-(1-methylethyl)-, (αR)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-α-(1-methylethyl)-, (R)-
OTHER NAMES:
CN **(+)-(R)-Verapamil**
CN (+)-Verapamil
CN **(R)-Verapamil**
CN d-Verapamil
CN Dexverapamil
CN R-(+)-Verapamil
FS STEREOSEARCH
MF C27 H38 N2 O4
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMLIST, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSRESEARCH, IPA, MRCK*, PHAR, PROMT, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological

study); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); FORM (Formation, nonpreparative); PRP (Properties); USES (Uses)

Absolute stereochemistry.



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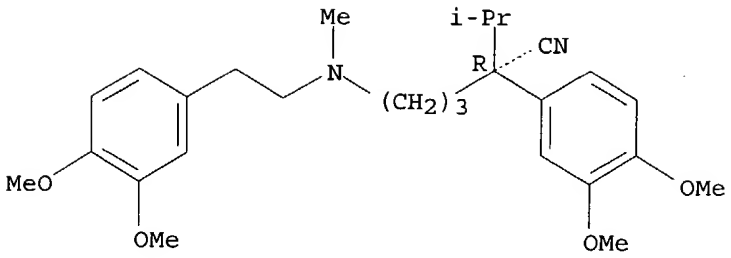
360 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
360 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 38176-02-2 REGISTRY
CN Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-α-(1-methylethyl)-, monohydrochloride, (αR)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-α-(1-methylethyl)-, monohydrochloride, (R)-
OTHER NAMES:
CN (+)-Verapamil hydrochloride
CN **(R)-Verapamil hydrochloride**
CN Dexverapamil monohydrochloride
CN LU 33925
CN NSC 632821
FS STEREOSEARCH
MF C27 H38 N2 O4 . Cl H
LC STN Files: BEILSTEIN*, BIOTECHNO, CA, CAPLUS, CHEMCATS, CHEMLIST, EMBASE, IPA, MRCK*, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
CRN (38321-02-7)

Absolute stereochemistry.



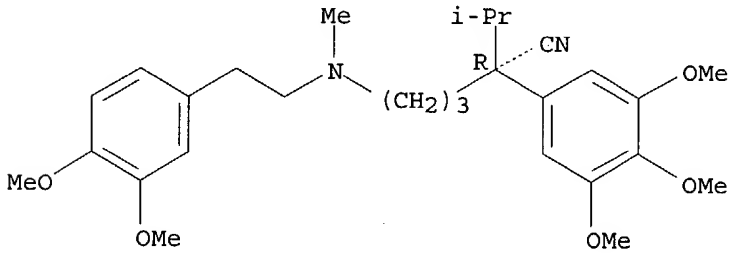
● HCl

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

27 REFERENCES IN FILE CA (1907 TO DATE)
27 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L4 ANSWER 3 OF 8 REGISTRY COPYRIGHT 2004 ACS on STN
RN 38176-10-2 REGISTRY
CN Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4,5-trimethoxy-α-(1-methylethyl)-, (αR)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4,5-trimethoxy-α-(1-methylethyl)-, (R)-
OTHER NAMES:
CN (+)-D 600
CN **(+)-Gallopamil**
CN (+)-Methoxyverapamil
CN d-D-600
CN **R-(+)-Gallopamil**
FS STEREOSEARCH
MF C28 H40 N2 O5
CI COM
LC STN Files: BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS, CASREACT, CHEMCATS, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)

Absolute stereochemistry. Rotation (+).



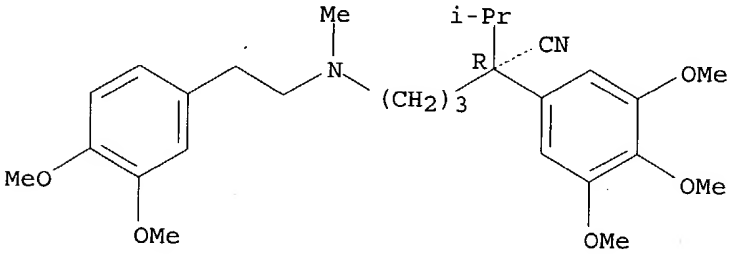
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

61 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
61 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L4 ANSWER 4 OF 8 REGISTRY COPYRIGHT 2004 ACS on STN
RN 38176-09-9 REGISTRY
CN Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4,5-trimethoxy-α-(1-methylethyl)-, monohydrochloride, (αR)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4,5-trimethoxy-α-(1-methylethyl)-, monohydrochloride, (R)-
OTHER NAMES:
CN **d-Gallopamil hydrochloride**
FS STEREOSEARCH

MF C28 H40 N2 O5 . Cl H
LC STN Files: BEILSTEIN*, CA, CAPLUS, MRCK*, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: PREP (Preparation)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); USES (Uses)
CRN (38176-10-2)

Absolute stereochemistry. Rotation (+).



● HCl

6 REFERENCES IN FILE CA (1907 TO DATE)
6 REFERENCES IN FILE CAPLUS (1907 TO DATE)

adjuvant

**Ad´ju`vant** Pronunciation: ăd´jū`vant

Noun 1. adjuvant - an additive that enhances the effectiveness of medical treatment
- additive - something added to enhance food or gasoline or paint or medicine

Adj. 1. adjuvant - relating to something that is added but is not essential; "an ancillary pump"; "an **adjuvant** discipline to forms of mysticism"; "The mind and emotions are auxilliary to each other"
- accessory, adjunct, ancillary, appurtenant, subsidiary, auxiliary
- supportive - furnishing support or assistance; "a supportive family network"; "his family was supportive of his attempts to be a writer"

2. adjuvant - enhancing the action of a medical treatment; "the **adjuvant** action of certain bacteria"
- materia medica, pharmacological medicine, pharmacology - the science or study of drugs: their preparation and properties and uses and effects
- helpful - providing assistance or serving a useful function

Legend: Synonyms | Related Words | Antonyms

Some words with "adjuvant" in the definition:

accessory	appurtenant
additive	auxiliary
adjunct	Coadjuvant
ancillary	subsidiary

Previous		General Dictionary Browser	Next
Adjutancy	Adjutator	Adlai Ewing Stevenson	Adlumia fungosa
adjutant	Adjute	Adlai Stevenson	adman
adjutant bird	Adjutor	Adlegation	Admarginate
adjutant general	Adjutory	Adlocution	admass
adjutant stork	Adjutrix	Adlumia	Admaxillary

Full Dictionary Browser

adjusting entry	Adjutant (enc.)	Adkins v. Children's	Adleman (enc.)
Adjusting plane	adjutant bird	Hospital (enc.)	Adler Planetarium (enc.)
adjustive	adjutant general	ADL (comp.)	Adler, Alfred (enc.)
Adjustment	adjutant stork	ADL (enc.)	Adler-32 (enc.)
Adjustment (law)	Adjutant-general (law)	Adlai E. Stevenson (enc.)	Adlet (enc.)
adjustor	Adjutator	Adlai Ewing Stevenson	AdLib (enc.)

Adjutage
Adjutancy
Adjutant
Adjutant (law)
Adjute
Adjutor
Adjutory
Adjutrix
Adlai Ewing Stevenson (enc.)
Adlai Stevenson
Adlai Stevenson (enc.)
Adlai Stevenson II (enc.)
Adlegation
Adlington (enc.)
Adlivun (enc.)
Adlocution
AdLog (comp.)

Definition of Adjuvant

Ad´ju`vant Pronunciation: ăd´jũ`v*a*nt

n. 1. *(Immunology)* A substance added to an immunogenic agent to enhance the production of antibodies.

2. A substance added to a formulation of a drug which enhances the effect of the active ingredient.

a. 1. Helping; helpful; assisting.

n. 1. An assistant.

2. *(Med.)* An ingredient, in a prescription, which aids or modifies the action of the principal ingredient.

Related Words

accession, accessory, accompaniment, addenda, addendum, additament, addition, additive, additory, additum, adjunct, alterative, analeptic, ancillary, annex, annexation, appanage, appendage, appendant, appurtenance, appurtenant, assistant, assisting, attachment, augment, augmentation, auxiliary, carminative, coda, collateral, complement, concomitant, continuation, contributory, corollary, corrective, counterirritant, curative, emmenagogue, expectorant, extension, extrapolation, fixture, fostering, healing, helping, hormone, iatric, increase, increment, instrumental, maturative, medicative, medicinal, ministerial, ministering, ministrant, nurtural, nutricial, offshoot, pendant, reinforcement, remedial, restorative, sanative, sanatory, serving, side effect, side issue, subservient, subsidiary, supplement, synergistic, tailpiece, therapeutic, theriac, undergirding, vasodilator, vitamin

Adjutant
Adjutant general
Adjutator
Adjute
Adjutor
Adjutory
Adjutrix